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URIC ACID

AS A

FACTOR IN THE CAUSATION OF DISEASE.

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URIC ACID

AS

A FACTOR IN THE CAUSATION OF DISEASE

A CONTRIBUTION TO THE

PATHOLOGY OF HIGH BLOOD PRESSURE, HEADACHE, EPILEPSY, MENTAL DEPRESSION, PAROXYSMAL HÆMOGLOBINURIA AND ANÆMIA, BRIGHT'S DISEASE, DIABETES, GOUT, RHEUMATISM,

AND OTHER DISORDERS

BY

ALEXANDER HAIG, M.A., M.D.Oxon., F.R.C.P.

PHYSICIAN TO THE METROPOLITAN HOSPITAL, AND THE ROYAL HOSPITAL FOR CHILDREN AND WOMEN; LATE CASUALTY PHYSICIAN TO ST. BARTHOLOMEW'S HOSPITAL

Fourth Edition

WITH SIXTY-FIVE ILLUSTRATIONS

LONDON

J. & A. CHURCHILL

7, GREAT MARLBOROUGH STREET

1897

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PREFACE TO THE FOURTH EDITION.

AGAIN a call for a new edition finds me in the position of being obliged to increase the size of the work, partly to put in new investigations, and partly to publish fresh portions of old work in reply to criticisms by fellow-workers; but I hope that in both ways the value of the record has been increased.

I may say also that each figure, and generally also each case is merely a sample, as it would require several volumes of this size to publish my researches in full.

Among the additions I may mention those on the action of uric acid on the blood, on the diurnal variations of the blood decimal, on the treatment of chlorosis; on the causation of high blood pressure by uric acid; the demonstration of uric acid and xanthin in the blood; the effects of wines, acids and alcohol on the acidity of the urine; the accidental causation of endocarditis by drugs; the urinary excretion over four years on various diets, and some recent experiments on diet with deductions as to the diet treatment and the best methods of altering it.

As will appear from the text many of my old friends continue to take a practical interest in the work, and to forward notes and contributions which are often of great value to illustrate special points, and to these I would once more tender my most hearty thanks.

There are also an increasing number of those who are interested, and I have reason to think that many more are finding both the theory and treatment useful in their daily work; to these also I would offer my thanks for the past, and my hopes for the future.

To Dr. E. G. Horder my special thanks are due for much kind help in the tedious work of revising proofs, and for other contributions.

7, *Brook Street*,
London, W.,
December, 1897.

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PREFACE.

THIS is practically a *résumé* of the facts and arguments in some twenty-five papers, on the subjects which form the headings of the chapters, which have appeared in various journals, transactions and reports from the year 1884 to the present time, together with such alterations and additions as further experience has suggested.

As my investigations tend to show that the functional and organic disorders of which I speak are in many cases entirely due to an excess of uric acid in the body and blood, this is practically a work on the causation of disease by uric acid, of the process by which it comes to be present in excess in the body, and of the means of preventing such excess.

I nevertheless regard the investigation at which I have been working during these years as only in its very first stages, and this volume as a mere preliminary communication, and one which was only undertaken because I felt that papers thus scattered about in various journals did not do the subject justice; and it is certainly not with any feeling that the matter is ripe for final judgment that I now put it forward.

Considerations of space have compelled me to give in mere outline much of the results of my work during the last six years, but any portions which the future may show to be of value can easily be recorded at greater length. It would also have been almost impossible to carry through the thread of my argument if greater details had been given here.

My most hearty thanks are due to Dr. Lauder Brunton for much kind assistance, advice and encouragement, and my readers will doubtless see that the investigation has not been by any means devoid of difficulties and doubts, though some of these now seem to have been happily surmounted.

I am also under considerable obligation to Sir Dyce Duckworth for allowing me to investigate certain interesting cases and for much kindly notice and instructive criticism of my researches in his work on "Gout"; also to Dr. Norman Moore and Dr. Ormerod for per-

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mission to work in the departments under their charge at St. Bartholomew's Hospital, and to my colleague, Dr. H. H. Tooth, for permission to quote some cases, and for much assistance in studying epilepsy from my point of view.

I have also to thank Mr. J. E. Saul, F.I.C., for kind help in several places in regard to points in chemistry where I should otherwise have been at fault, and to many others who, as appears in the text, have helped me by permission to study their cases, copy their notes, or profit by their experiences, I must here also return my grateful thanks.

7, *Brook Street,*
Grosvenor Square, W.,
February, 1892.

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URIC ACID

AS A

FACTOR IN THE CAUSATION OF DISEASE.

CHAPTER I.

History.

It is now fifteen years since I began the research of which I propose to give an account in the following pages.

It seemed to me then a small and simple matter to investigate the causation and treatment of the headache from which I suffered; but gradually through these years the horizon has expanded, and I now see that if even a half of my deductions are eventually substantiated, a very large portion of the field of medicine will be modified thereby.

It will easily be understood, then, that I am not here attempting any complete and finished picture; but as it has seemed to me that my results being published as yet in several journals and at various times, the subject has never presented to those who may have read my more or less isolated papers the same cohesion and strength which a survey of the whole field, even though necessarily incomplete, may afford, I shall endeavour to remedy this defect by giving as shortly as possible a consecutive statement of the main points.

Having been all my life a sufferer from migraine it was in the autumn of 1882 that in despair of obtaining any complete relief from drugs, and not without some fear that I was really suffering from organic disease, I gave up all butcher's meat and replaced it by milk and fish, the latter in decreasing quantities till milk and cheese formed, as they do now, my only animal foods.

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I had previously tried a great variety of alterations in diet, including an increased allowance of meat and various alterations in quantity and quality of less important constituents, such as sugar, tea, coffee, and tobacco, without any noticeable result. But on the non-meat diet a change was at once apparent; my headaches diminished both in frequency and severity, and from an average of one in a week they fell steadily, as the diet was persevered in, down to one in a month, one in three, six, eight, or twelve months, and eventually eighteen months elapsed without an attack of notable severity.

Since that I have never gone back to butcher's meat, and I never intend to, because by avoiding it I obtain what is practically immunity from a disorder which, at one time, bid fair to cripple me and prevent completely all mental and sedentary work; not that the headache was confined to periods of sedentary work, for I have often had to give up portions of a day's shooting because my head was too bad to stand the noise and concussion of firing, and yet this was in the open air of the country, and when a book had probably not been open for weeks, and under conditions which were infinitely more favourable to health than those in which I now exist and have immunity.

But if I at any time forget my lesson of the past and presume on my apparent security from attack, if I dine with two or three friends in the same week, and especially if I take both meat and wine, of the action of which I shall speak presently, I am practically certain to have a more or less severe headache in two or three days' time; though, as will appear further on, I can generally prevent the intense pain from which I used to suffer in former days.

Having arrived, then, at the conclusion that leaving off butcher's meat had practically relieved me of headache, I began to ask why this was so, and at first (*Practitioner*, 1884), I was inclined to attribute it to the formation of some poison possibly of the nature of a ptomaine, in the intestines during the digestion of the butcher's meat.

But a further study of the clinical history of migraine brought out such a strong relationship to gout, that (*Practitioner*, 1886), I began to suspect that uric acid might be the poison of which I was in search, and I therefore proceeded to estimate the excretion of uric acid and urea.

At first I estimated only the excretion of twenty-four hours, and as many of my headaches lasted only a portion of a day, I got indefinite or contradictory results; but when I separated the urine

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excreted during the headache from that both before and after it, a definite and distinct relation between the headache and the excretion of uric acid at once became apparent—a relation which I have since found both in myself and others, in very numerous instances, quite sufficient to remove the result out of the chapter of accidental coincidences. But the headache in question, as described by Liveing and others, has other important concomitant symptoms—as slow high tension pulse, cold surface and extremities, mental depression, and disinclination for exertion, mental or bodily, and the urine during the headache is scanty and of high colour and specific gravity.

But once having noticed the relation of this headache to the excretion of uric acid, I soon noticed that each of its concomitant symptoms bore exactly the same relation to uric acid, that when the pulse was slow and of high tension there was always a greater excretion of uric acid than when it presented the opposite character, and the same with the mental depression and scanty urine.

After this a little further experimentation brought out the fact that the excretion of uric acid was completely within my control, and that I could alter it from day to day or hour to hour in either direction at pleasure (*Journal of Physiology*, vol. viii.).

I now soon found out that in altering the uric acid I could alter the symptoms related to it; that when I produced an increased excretion with alkali, I produced the headache, mental depression, cold surface, slow pulse and scanty urine, and that when I stopped the plus excretion with an acid I removed all these symptoms; so that not only had I acquired the power to produce or remove the headache, but I had also the power to relax or contract the arterioles and capillaries, to affect the tension of the pulse, the rate of the heart's action, and thus to influence the circulation in the brain, skin, kidneys, and probably the whole body.

Then I also soon noticed that in curing a headache by giving an acid to diminish the excretion of uric acid, I always produced a certain amount of pricking and shooting pain in my joints (generally in those which had been most used on the day in question), and it naturally occurred to me that the uric acid was held back in these joints and produced the pains. The uric acid which failed to appear in the urine must have gone somewhere. What more natural than to suppose that it had been retained in the joints (where in gout it is found), and that the pricking pains were the evidence of its presence?

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Then on turning to Sir A. Garrod, I found that he had described precisely similar joint pains as occurring in gouty subjects immediately after the injestion of beer or wine, and a very little investigation sufficed to prove that all beers and wines are strongly acid, so that a very simple explanation could be given of the facts.

Since that I have found not only that an attack of gout or rheumatism can be produced by giving acid, but that what I had observed was only a single instance of a general law, and that all substances which increase the solubility of uric acid increase its excretion in the urine, and do good in those joint troubles which are due to its irritating presence; while conversely, all substances which diminish the solubility of uric acid, diminish its excretion in the urine, and also increase those irritations in joints and other fibrous structures which are due to its presence.

On such comparatively simple facts and observations the whole of my writings have been based, and as side issues I have been led to reason on the pathology of epilepsy, in some cases of which I found exactly similar fluctuations in the excretion of uric acid to those met with in migraine, thus explaining a clinical relationship between these two diseases which had long been known and written about—also on the pathology of rheumatism and rheumatoid disease, the causation of Bright's disease, Raynaud's disease, and paroxysmal hæmoglobinuria and anæmia.

But if uric acid affects the arterioles or capillaries in the way and to the extent which I claim that it does, it will easily be understood that it must influence for good or evil the function, nutrition and structure of every organ and tissue of the body, from the skin outside to the most central fibres of the spinal cord and brain within. And when they have looked carefully into the effects which uric acid produces in the causation of fatigue, and the way in which it brings about a rise or fall in the formation and excretion of urea, I think that no one will have any difficulty in admitting its enormous power over the metabolism of the whole body.

Naturally the subject is not so simple as might appear from this outline, but that will be sufficiently evident when we come to deal with the points in detail, and I shall endeavour as far as possible to conduct my reader through the same course of reasoning that I myself followed, so that I may escape the omission of any important points.

Before going on to do this I shall just mention shortly some passages in the writings of Sir A. Garrod, Dr. Liveing and others, which have had important influence in shaping the course of my investigations.

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Sir Alfred Garrod says ("Gout and Rheumatic Gout," ed. iii., p. 6): "Galen, who lived about the latter half of the second century, was of opinion that gout was caused by some unnatural accumulation of matters in the part affected. These matters were supposed to consist of phlegm, bile, blood, or a mixture of these fluids, and chalk-stones were considered to be formed by their concretion or solidification."

Our knowledge now at the end of the nineteenth century, might be expressed in almost the same words if we substitute "uric acid" for "phlegm, bile and blood."

On a previous page Sir A. Garrod says (p. 2, prev. ref.): "It is by no means rare to hear of inflammation of a joint by one practitioner called gout, by another rheumatism, and by a third rheumatic gout," and if it should appear in the following pages that my work tends to show that these more or less distinct clinical conditions may all be due to accumulation of uric acid, I hope this will not be regarded as a step backward, but rather as an advance, in that, with greater knowledge of the chemical and physical properties of uric acid, we are now able to understand how it may produce very different clinical pictures according to the time during which it acts, according to the quantity in which it is present, and according also to the metabolic activity as well as the structure, vascularity and general anatomical arrangement of the tissue on which it acts.

And we may think rather that the discrepancies of opinion which Sir A. Garrod mentions reflect credit on our profession, who failed to detect essential differences where nature had placed none. Further on Sir A. Garrod says (p. 275), "The causes which predispose to gout independently of individual peculiarity are either such as produce an increased formation of uric acid in the system, or lead to its retention in the blood."

And in the Lumleian Lectures (*British Medical Journal*, January, 1883, p. 549), he says, "May it not be the case that when uric acid exists in the blood it is attracted differently by different organs, and thus the spleen and liver more frequently contain appreciable quantities than other tissues? Or, again, may it not be that in some organs as the spleen, the substance of which, if not acid during life rapidly becomes so after death, while the blood remains strongly alkaline the uric acid becomes less soluble and more easily retained."

I shall presently show how I was led by my results, and without any knowledge of Sir A. Garrod's remarks, to believe that excess of uric acid in the blood and body are almost never due to increased formation, but generally to failure of excretion or retention; and that

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then, having observed that I was always able with alkalies to increase, and with acids to diminish, the excretion, I adopted (*Journal of Physiology*, vol. viii.) Sir A. Garrod's above-quoted suggestion to explain my results, and have continued to use it ever since.

With regard to lead Sir A. Garrod says (p. 243), "It would appear, therefore, that in individuals impregnated with lead the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion."

My researches seem to me to show that the blood never becomes loaded with uric acid except as the result of excessive introduction followed by or acting in conjunction with imperfect excretion, and such imperfect excretion or retention is sufficient to account for the largest quantities I have ever seen in the human body, so that there is no need of excessive formation as an explanation. I do not assert that excessive formation never occurs, but only that I have not met with any conclusive proof of its occurrence, while all the phenomena of disease can be completely explained by the ordinary formation of uric acid, plus a certain quantity of it introduced ready formed in food, without postulating the excessive formation of a single grain (see fig. 64).

Sir W. Roberts says ("Urinary and Renal Diseases," ed. iv., p. 73): "It may be regarded as probable that the defective power of the kidneys to eliminate uric acid in gout arises from a diminished alkalescence of the blood."

From my point of view it has nothing whatever to do with the kidneys; the urates are not in solution in the blood, and are not brought to them; when they have been got into solution by an alkali and come to the kidneys they are excreted fast enough.

But neither Sir A. Garrod nor Sir W. Roberts knew what I found out, that the excretion of uric acid can be made to vary at any time and in any direction—a discovery which not only enabled me to explain all the symptoms of the uric acid headache, but also showed me the way in which, by the gradual accumulation of small quantities, very large amounts of urate come eventually to be stored or retained in the body without any excessive formation having taken place. It also showed me that the daily physiological fluctuations in the excretion of uric acid are due to the same cause, and depend on the amount of solvent alkali in the circulation, the greatest excretion of the day occurring in what Sir W. Roberts has called the "alkaline tide," and the smallest excretion in the high acidity period of the night.

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And not only is this so, but it is easy to demonstrate that this well-known large excretion in the "alkaline tide" is not due to formation; for if a dose of alkali is taken at bed time for several nights, there is an increased excretion of uric acid during the night, and then the "alkaline tide" excretion is correspondingly diminished till after a few days the hourly excretion is almost equal all through the day and night.

I would like to add here one word to express my great respect for the magnificent work of Sir A. Garrod, which, founded as it is on experimental research of the most accurate kind, must for a long time to come remain a landmark for all those who work at uric acid.

And if in a few points I have ventured to give other explanations of the facts than those he suggests, or to think that in some few of his results he may have been misled by the working of a less perfect process than that I have used, that has never prevented me from seeing how greatly I am indebted to the careful records of his experimental work, and to his valuable suggestions founded upon it.

To Dr. Liveing's very interesting work on headache I am indebted, not only for a knowledge of the relationship of migraine to gout, but also for that of the relationship of migraine to epilepsy and of both to gout, and it was his quotation from du Bois Reymond and others that led me to look for a uric acid reaction in epilepsy similar to that I had found in migraine.

Since the first edition of this book appeared (1892) I have made two discoveries with regard to the causation of disease by uric acid: first of all I found that uric acid taken by the mouth passes into the blood, and that if this fluid is kept in a condition to hold it in solution, it will remain in the blood till the kidney has time to pass the whole of it into the urine; so that of 12 grs. taken by the mouth some 10 or 11 grs. can be obtained from the urine within three or four days after it has been swallowed. (See *Journal of Physiology*, vol. xv., p. 167.) Now this brings to the front two important points: (1) That the uric acid excreted normally in the urine comes from two sources, (α) the uric acid formed in the body out of nitrogenous food and (β) the uric acid introduced into the body in meat, meat extracts, soup, tea, coffee, &c., all of which contain it in considerable quantity. (2) That in so far as the morbid processes of which I shall speak in the following pages are due to an excess of uric acid in the blood, they can be produced at pleasure simply by taking that substance by the mouth, and thus any one who wishes to do so can repeat my experiments and satisfy himself as to their truth.

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As regards the quantity of uric acid in meat, meat extracts, soup, &c., it is necessary to bear in mind the following points:—

Not to go deeply into theoretical chemistry, it may be said that Haycraft's process for the estimation of uric acid in urine, which I have used throughout my researches, estimates as uric acid not only the uric acid present in that fluid, but also a certain amount of xanthin, hypoxanthin or other members of the xanthin group.

This process, therefore, estimates the amount of uric acid too high in proportion to the amount of these xanthin bodies present; but inasmuch as urine contains only very small quantities of these xanthins the error from this source, so long as the process is applied to urine, is not great.

When, however, the process is applied to extracts of muscle, blood and other tissues, which contain considerable quantities of these xanthin bodies in addition to a little uric acid, the error may obviously be very large indeed, and what is reckoned as uric acid may not chemically speaking be that substance at all.

If this was a work on Physiological Chemistry, the error thus introduced would no doubt be a very serious one. I shudder to think of the number of atoms of oxygen that I have inadvertently added on to the xanthins contained in muscle by reckoning them as uric acid.

But as we are dealing with physiology and pathology alone, it is easy to show that the chemical inaccuracy above mentioned is a matter of no consequence, indeed it has probably been an advantage, for as I have pointed out it makes absolutely no difference to physiological and pathological results whether a man swallows two grains of hypoxanthin, xanthin, caffeine, theobromine, or uric acid itself; all these substances alike produce obstructed capillaries, high blood pressure, headache, mental depression, scanty secretions and a large excretion of a substance estimated as uric acid in the urine by Haycraft's process.

On the other hand, if I had estimated only the true uric acid in muscle, I should have quite missed the explanation of its physiological and pathological effect, and we must not forget the points mentioned at the beginning of the chapter, that my whole research originated with my observation that a certain form of headache is made worse by eating meat, meat soup, or meat extracts, and is cured or prevented by abstaining from them.

If physiological chemistry is correct, muscle contains only a very small quantity of true uric acid, but a considerable quantity of xanthins which are physiologically and pathologically identical with

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it, and differ from it chemically merely in the absence of one or more atoms of oxygen.

The explanation is therefore complete; meat produces the headache by introducing into the body and blood uric acid plus substances of the xanthin group, and the same headache can be produced at will by swallowing any one of these substances in a state of comparative chemical purity.

I have all along felt that in applying Haycraft's process to extracts of tissues I was walking on dangerous ground as regards theoretical chemistry, and I have, therefore, been careful to point out (ed. ii., p. 355) that, while I gave figures of the amount of uric acid found in various animal foods by this process, the only satisfactory test of the amounts of these uric acid compounds contained in them is the physiological one of eating a known quantity of the substance in question and watching the effects on excretion in the urine (see eggs in chapter on Treatment.) And this can be done without any fear even of theoretical chemistry, for as xanthin, hypoxanthin, &c., have only been found as mere traces in urine, it follows that the relatively considerable quantities of these substances contained in meat food, must be largely converted into uric acid by the addition of oxygen in their passage through the body.

My second discovery, which was to a large extent a result of the first, was that uric acid when present in excess in the blood affects its quality in an important manner, producing the changes met with in anæmia, paroxysmal hæmoglobinuria and other diseases, and also counteracting the effects of iron and preventing it from building up the blood and curing these diseases.

Thus I found not only that by administering uric acid I could control the value of the blood decimal (hæmoglobin divided by red cells) in myself and others, but that my own blood decimal actually varies from day to day, and even from hour to hour (see fig. 45) in accordance with the quantity of uric acid passing through it into the urine. We shall also see in the following chapters that uric acid affects not only the blood, but influences in a similar way the function, nutrition, and eventually the structure of every organ and tissue in the body, and as regards infectious diseases has in some cases a more important influence, than the microbes themselves. As regards the tissues, it controls not only their nutrition but also their great physiological functions, the production of energy and the production of heat, to an extent which, acting as it does from hour to hour throughout the whole of life, cannot but be of enormous importance.

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CHAPTER II.

Formation and Excretion of Uric Acid.

One of my early observations on the excretion of uric acid and its relation to a headache showed that while there might be a bad headache one day, with, say, an excretion of 16 grs. of uric acid in the twenty-four hours, there might be an exactly similar excretion on another day without any headache whatever, and viewing only the absolute excretion of uric acid these observations appear to be contradictory and prove nothin .

It was always necessary, however, to view something besides the absolute excretion of uric acid, viz., its relation to urea, and when this was done a difference between these two days at once came out. On the day when 16 grs. were excreted without a headache, the relation of uric acid to urea was 1—33 (one of uric acid to 33 of urea), but on the day when, with a similar absolute excretion of uric acid there was a severe headache, its relation to urea was 1—18 or 1—20.

The uric acid excretion in the uric acid headache is not only absolutely large, but it is greatly in excess of its normal relation to urea. Before going further we may try to determine what is the normal relation of uric acid to urea in excretion, and also if possible in formation.

My researches have extended over a large part of the last twelve years, but taking only the figures of the longer periods of my estimation of my own excretion, we get a total of 2,351 days in which 28,447 grs. of uric acid, 805,432 grs. of urea, and 127,725 grs. of acid (reckoned as oxalic acid) were excreted; giving a relation of uric acid to urea of about 1—28, and a relation of acid to urea of 1—6·3.

These figures divided by the number of days give uric acid 12 grs., urea 342 grs., and acidity 54 grs. per day. I must explain that my urea at the present time runs at from 375 to 437 grs. per

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day, or from 3 to 3½ grs. per pound, and that the low urea in the totals just given is the result of my having attempted to diminish my nitrogen during several years, which are included in the above totals (see fig. 64).

Now however that I know that the uric acid which caused my troubles was to a large extent due to direct introduction, I can easily keep my urea about the physiological level by eating substances which contain sufficient nitrogen, but which introduce into the body little or no uric acid or xanthin (see chapter xvii.).

But the total uric acid is increased probably by about 160 grs. swallowed intentionally for experimental purposes, and say some 300 grs. which were stored in the body before the estimation of the excretion began. (Thus I have calculated from the per centage of urate found in the various organs and tissues after death, multiplied by the weight of these tissues in the body that a man of 12 stone would probably have 300 grs. in his various organs and tissues. And as this is probably not an over-estimate I have put down 300 grs. as the quantity in my own tissues, but it must be understood that the calculations I am now making are provisional merely and subject to revision as our knowledge becomes more accurate.)

Subtracting the 460 grs. thus accounted for from the total of 28,447 grs. we get 27,987 grs. as representing the excretion of uric acid in the above 2,351 days, apart from the urate which was intentionally introduced, and apart from that which was already present in the body when the experiment began. This gives a daily excretion of 11·9 grs. of uric acid and a relation of uric acid to urea of about 1—28·7.

But the daily excretion equals the daily formation plus the daily introduction of urate ready formed in the food; and though my food is probably much poorer in urate than that of persons on ordinary diet with an ordinary allowance of butcher's meat, soups and meat extracts, still there seems to be little doubt that my food does contain some uric acid or other members of the xanthin group equivalent to it. Let us say, for the sake of getting even figures, that I introduce or did introduce during some periods of my research with my food 1·9 grs. of uric acid per day, and subtracting this from the 11·9 grs. of daily excretion we get 10 grs. of uric acid as the actual quantity of the substance daily produced in my body out of nitrogen introduced into it in other forms, the remainder of this nitrogen furnishing about 342 grains of urea, giving a relation of uric acid to urea of 1—34.

Let us now try and work out the formation and excretion of a

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man of 150 lbs. from these data. Let us say that he forms 3·5 grs. per lb. of urea = 525 grs. a day, and uric acid in relation of 1—35 = 15 grs. per day. Then he will introduce in his food perhaps 1 gr. of uric acid per 100 grs. of urea = 5·25 grs. Therefore the total uric acid formed and introduced will be 20·25 grs. a day, and if he excretes the whole of this uric acid it will hold the relation to urea of 1—26. But this man with higher introduction of uric acid will have diminished alkalinity of blood, and with this, and depending upon it, lessened solubility and excretion of uric acid, that is to say, he will not excrete all the uric acid introduced in his food or formed in his body, but will retain a portion of it in his body. So that while I, in 2,351 days, have probably washed out of my tissues and excreted some 300 grs. of uric acid because my acidity has been low, this man with higher acidity may have retained in his tissues in the same period some 300—400 grs.

Such a man, instead of excreting the full 20·25 grs. of uric acid which is formed and introduced into his body each day, will only excrete, say, 19·5—20·0 grs., retaining in his tissues the remaining ·2—·7 of a grain., which in the course of years will amount to many hundreds of grs., and the higher the acidity the greater the proportionate retention will be.

I consider, therefore, that every man who eats what is called ordinary diet with butcher's meat twice a day, and also drinks acid wines or beer, will, by the time he is 35 or 40, and certainly by the time he is 50, have accumulated 300—400 grs. of uric acid in his tissues, and possibly much more; and about this time, owing to the large amount of uric acid in his body, he will probably be subject to attacks of some form of gout or chronic rheumatism.

If such a man is killed by accident at this time, a quantity of uric acid, more or less equivalent to the above-mentioned amounts, will be found in his tissues. If, on the other hand, he dies slowly after several years of wasting disease very much less will be found, for during his wasting there will be a marked fall of urea and acidity, his blood will become more alkaline and will take up uric acid from his tissues and pass it in excess in his urine. This is the reason we find erosions with but little urate deposit in the joints of patients who have died of wasting diease; before these patients began to waste all the erosions were no doubt full of it.

If the blood of such a patient suffering from wasting disease is examined every few weeks a steady and continuous fall of the blood decimal (see chapter xii.) will be found corresponding to the amount of uric acid passing through the circulation, and this is no

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doubt the secret of the causation of much of the anæmia of old age and wasting disease.

In most cases of wasting disease the plus excretion of uric acid, and the excess passing through the blood produces symptoms which it is generally easy to recognise, such as slow high tension pulse, with some headache and mental depression, and I doubt not that in the more or less physiological conditions of mere old age an excess of uric acid in the blood having a similar causation plays an important part.

With regard to the relation of uric acid to urea in excretion, namely, 1—33 or 1—35, other investigators, Messrs. Yvon and Berlioz (*Rev. de Med.*, September, 1888), found as the result of one series of experiments the relation 1—30, and of another series 1—40; while Lecanu (quoted by Sir Dyce Duckworth, "A Treatise on Gout," p. 120) found much the same relation that I have, viz., 1—33.

There is thus a considerable collection of figures tending to show that the normal relation of uric acid to urea in excretion is 1—35 or thereabouts, and I have ventured to suggest that where this has been found over a very long period of time, it may represent something near the real relative formation of these two substances. It is probable, however, that these results as found by myself and others all include a considerable quantity of uric acid which is introduced with the food and not formed in the body, so that the real ratio of formation in man may be nearer 1 of uric acid for 40 of urea.

As already mentioned (chapter i.) I have adopted the theory of Sir A. Garrod, that the final stage in the formation of uric acid is the production of urate of ammonium in the kidney.[1]

According to this theory a large part of the urate so formed passes at once down the ureter and is excreted; but a small residue lingers in the kidney or the blood circulating in it, and is eventually carried over by the renal vein into the general circulation; when there it is, according to the same authority, attracted differently by different organs, and tends to be rendered less soluble, and so to be held back and accumulate in certain

[1] Sir A. Garrod also read a paper before the Royal Society, in 1893, in which he shows that there is urea in the blood of birds though their urine contains none. He concludes, I believe, that in birds, just as in man, uric acid is formed in the kidney out of urea and other nitrogenous antecedents which come to it in the blood.

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organs, as the liver, spleen, and certain fibrous tissues, especially those of joints, probably because these tissues are less alkaline than the rest of the tissues and fluids of the body.

Now, it has long appeared to me that these theories of Sir A. Garrod would enable me to explain completely all my results regarding the excretion of uric acid; not to mention a whole string of disease processes of which, as we shall see presently, they afford an equally simple explanation.

We are now, however, in a position to return to our original question—why there is a headache one day with an excretion of 16 grs. of uric acid, and little or no headache another day, when an identical quantity is excreted.

Starting with the idea that uric acid might be the cause of the headache in question, it appeared to me that the above-mentioned theories of Sir A. Garrod not only favoured this idea, but afforded a very simple and complete explanation of the way in which an excess of uric acid in the blood was brought about.

Taking it that uric acid is never formed in greater relative proportion to urea than 1—33 (1 gr. uric acid for 33 grs. of urea), how comes it that on any given day uric acid can be excreted in the relation to urea of 1—18 or 1—20?

Obviously Sir A. Garrod's theories supply an explanation ready to hand. If 16 grs. of uric acid are excreted to-day, while judging from the urea excreted only 12 grains of uric acid were formed, then 4 grs. of uric acid must have come from some other source than the formation of this day, *i.e.*, must have been formed on some previous day, when, however, they were not excreted, but were held back and retained in the body—in the liver, spleen, joints, or fibrous tissues elsewhere.

And the curves which I have shown to illustrate various papers exactly bear this out. In my paper on "Headache" in the *Transactions of the Royal Medical and Chirurgical Society* I mentioned that the excess of uric acid on the day of headache was almost exactly made up and accounted for by the amount retained, as shown by the curve on the four or five preceding days (see fig. 38).

So that in so far as the headache was due to uric acid it was due to a fluctuation in its excretion, no alteration in formation having necessarily taken place, and we shall see presently that the action of various drugs exactly bears out this supposition.

When 16 grs. of uric acid were excreted with 528 grs. of urea (*i.e.*, in the nearly natural relation of formation 1—33) there was never any excess of uric acid in the blood, the whole 16 grs. of uric

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acid were formed that day in the kidney and passed with the urea at once down the ureter, and there was no headache because there was no excess of uric acid in the blood.

When, however, 16 grs. of uric acid were excreted with only 396 grs. of urea, a relation of 1—24·7, the whole of the uric acid was not formed in the kidney on this day, and some 4 grs. of it must have come from other parts of the body, as the liver, spleen, joints, in which we are supposing it to have been previously retained.

This uric acid, however, would pass through the blood on its way to the kidney, it would be for some hours in excess in the blood, and would give rise to headache and other signs of its presence, and this is, I think, a good and sufficient answer to our question.

Similarly any uric acid introduced into the body with the food will pass through the blood on its way to the kidneys, and one has to judge from other concomitant conditions which source (introduction or retention) the excessive excretion comes from.

In accordance with this reasoning I have always insisted that the relation of uric acid to urea in excretion is of very great importance, as it shows on any given day whether there has or has not been any temporary excess of uric acid in the blood, and the condition of the blood itself, either from hour to hour or day to day, can now be freely used as a further index of the same thing.

I would here just remind my readers that if one grain of uric acid is held back in the body every day, nearly one ounce could be so provided in a year, and though in nature such a thing would rarely happen, the balance of retention and excretion over a series of years may tend either to increase the stores or to gradually diminish them.

Fig. 1 shows the natural plus excretion of uric acid which occurs in everyone every day.

The exact hours in which it will fall depends upon their habits as to food, exercise, sleep, &c., because these control the daily fluctuations in acidity, and the acidity controls the excretion of uric acid. By altering completely the acidity of the whole day we can alter completely the excretion of uric acid also throughout the whole day.

In this figure we see that the curve of acidity is low at 8.45 a.m., and rises from this gradually up to 2.45 p.m.; after this it falls again, more or less decidedly, producing what I have called the second or afternoon alkaline tide.

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As a result of this low acidity in the a.m. and early p.m. hours, uric acid is above urea, and comes below it for the first time at 3.45 p.m.

We must bear in mind, however, that this high uric acid is dependent upon two factors—(1) the low acidity of the urine corresponding to high alkalinity of the blood and rendering that fluid a good solvent of uric acid, and (2) the presence somewhere in the body of a quantity of uric acid available for solution when the condition of the blood becomes favourable to this solution.

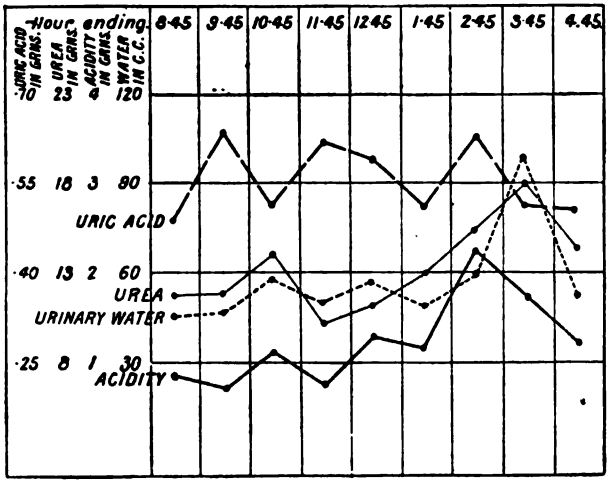

FIG. 1.—NATURAL PLUS EXCRETION OF URIC ACID IN THE ALKALINE TIDE.

Breakfast ended 9.50 A.M. Lunch ended 2.10 P.M. Two and a-half miles sharp walking 3.0 to 3.45 P.M.; perspiration, and low tension pulse after walk. Total urinary water 527 cubic centimètres. Total urea 118 grains. Total uric acid 5·0 grains. Relation of uric acid to urea 1 to 23·6.

If we have cleared out all the available uric acid by means of solvents, the acidity may fall much lower than it does in this figure without there being any plus excretion of uric acid (see fig. 64).

We shall see presently how there comes to be a store of uric acid in the body in the ordinary daily excretion; but it is of the first importance to bear the above-mentioned factors in mind, if we are to avoid misunderstanding and error in watching the daily and hourly excretion of uric acid.

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We see also in this figure that the urinary water is low all through the morning hours and rises for the first time at 3.45 p.m. when also for the first time uric acid is below urea.

So that this figure, like many others in this volume, serves to illustrate that relation between uric acid and water in excretion which I have ventured to formulate as a law—that the urinary water varies from hour to hour and day to day inversely with the excretion of uric acid or inversely with the height of the uric acid above the urea.

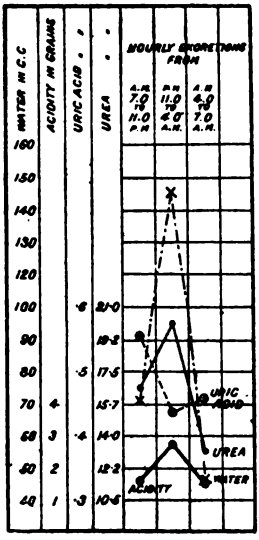

FIG. 2.—DAILY EXCRETION OF URIC ACID IN EPITOME.

We shall see later that other secretions and excretions bear an exactly similar relation to the amount of uric acid in the urine and blood, and that this law is of the utmost importance in enabling us to prove the power of uric acid over the circulation of the whole body.

Fig. 2 shows the daily excretion of uric acid, urea, water and acidity in epitome.

The total excretions of the hours placed at the top of each column are divided by the number of hours, so that the curves represent the average hourly excretion in each period.

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We see, then, that in the hours 7 a.m. to 11 p.m. (*i.e.*, the usual working day hours) uric acid is above urea, and water is low. Acidity is also low, and this is the cause of the high uric acid.

In the hours 11 p.m. to 4 a.m. acidity and urea have risen considerably, as a result of the high acidity uric acid has fallen considerably below urea, and as a result of this low uric acid, which means absence or relative absence of uric acid from the blood, the capillaries throughout the body have been freed, and as a result of these freed vessels in the kidneys there has been a free elimination of water from the blood and a diuresis, hence the urinary water is, as we see, very high.

The free capillaries all over the body produced everywhere quite definite and distinct effects, with some of which we shall have to deal at great length in other chapters, and it will then appear that part of the rise of urea is due to the fall of uric acid, and the free capillaries and increased metabolism throughout the body which are the results of this fall.

In the hours 4 a.m. to 7 a.m. we see that acidity falls to its lowest point, that urea falls very greatly, that water comes down also to its lowest point, and that uric acid rises.

The rise of uric acid is due to the fall of acidity, but it is also due to the retention of uric acid in the previous night hours.

When uric acid was low in the night there was no alteration in its formation relative to urea, it was being formed then as always in the relation to it of about 1 to 35; but the condition of the blood was unfavourable to its solubility, and a certain quantity of it was being held back and retained in some of the organs and tissues instead of being excreted in the urine, and the consequence of this was that the moment the acidity fell in the early morning hours, there was some uric acid available for solution in the blood, and this passing into the blood and urine raised the excretion of uric acid above urea, there being again no alteration in formation (relative to urea) whatever.

And this fact is susceptible of most simple demonstration, for if you administer sufficient alkali to prevent the rise of acidity in the night hours, you will find that there is then no excess of uric acid passed in the urine of the early morning hours.

But if the large excretion in the morning hours was due to new formation of uric acid, it is difficult to see how the previous administration of an alkali could possibly prevent this formation.

Further, if you gave an alkali so that there was no rise of acidity and fall of uric acid in the night hours, you would have also no

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diuresis in those hours; but the water would remain in the blood and body and pass out the next day whenever the supply of uric acid was exhausted, and it fell below urea from this cause.

I would ask my readers to give this matter their careful attention and to bear this small figure constantly in mind, as it is the key to

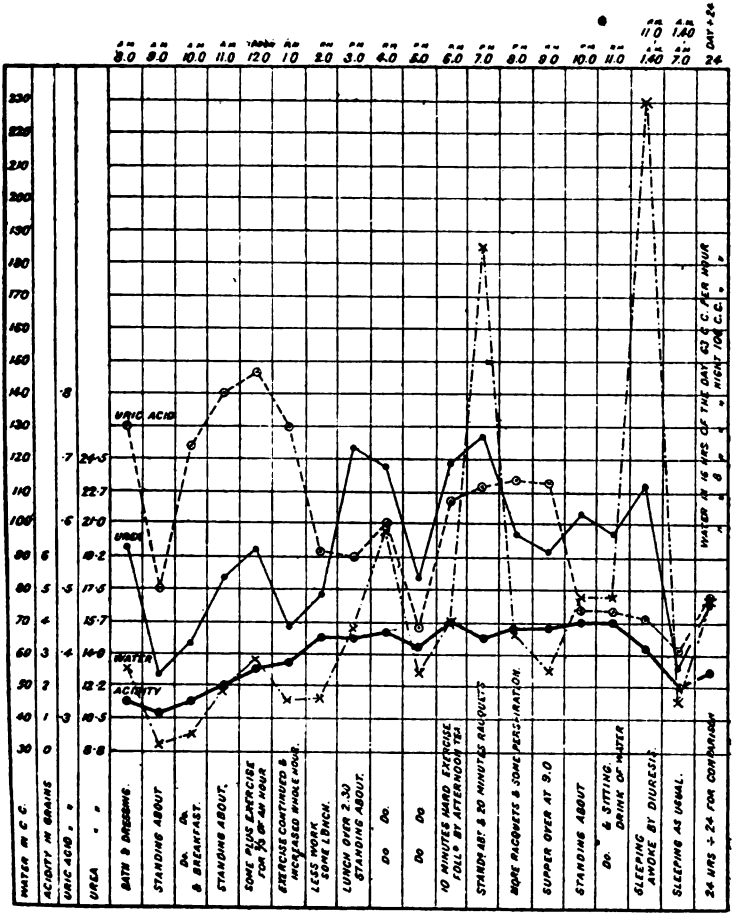

FIG. 3.—DAILY EXCRETION OF URIC ACID FROM HOUR TO HOUR.

nearly everything that follows. They will find also as a matter of experiment, that by controlling the acidity or the uric acid and producing changes in these such as are shown in the figure, they are able to control to a large extent the urea and to a still greater extent the urinary water, and that these are the signs and results of similar

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but more important control over the capillaries, the blood pressure, the action of the heart, and the physiology of the whole body.

Now the acidity can be controlled by the administration of acids and alkalies, by increase or diminution of activity and perspiration, (as in fig. 1), or by altered formation of urea (as in fig. 2), and by many things which indirectly affect these factors.

Uric acid can be controlled by the administration of many substances which increase or diminish its solubility in the blood; it can also be increased by direct administration of uric acid itself, or of xanthin or many of its compounds which are practically equivalent to uric acid.

In making any such experiment, however, it is necessary to bear in mind that the alterations in the curves of fig. 2 represent the resultants of a large number of forces, acting some in one direction, some in another, and that whatever substance is used to produce a given change, must be present in sufficient quantity to overcome other and opposing forces or there will be no result.

Fig. 3 shows much the same thing only at greater length. It gives the actual hour to hour excretions of the hours of the working day, but it was obviously impossible to divide the night without interfering so much with physiological conditions as to make the results of no value; and I had, therefore, to take such chance divisions as were possible. I have also added at the end the result of dividing the whole day's excretions by 24 so as to make it comparable to the hourly excretions and give us a standard or average by which to judge them.

We see then, much as in fig. 1, that uric acid is above urea all the morning hours and does not come below it till 3 p.m., and that with the exception of 8 and 9 p.m. and the early a.m. hours of the following day, it is below it all the rest of the twenty-four hours.

The average hourly excretion of uric acid is below ·5 of a grain or less than 12 grains in 24 hours, the highest hourly excretion is above ·8 grs., and the lowest but little above ·4.

Acidity and urea run fairly well together, though the urea fluctuates much more than the acidity. They agree in being low in the morning hours and high in the afternoon, evening, and early part of the night.

The relation of acidity to urea is as we have seen fairly constant over a long period of time at about 1 of acidity for 6·3 of urea, and it seems to me that this is due to their being two results of one and the same metabolism; that is to say, that

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every molecule of proteid material which in breaking up furnishes the constituents of urea, furnishes also at the same time certain acids, salts, or substances capable of oxidation which affect the acidity of the urine; thus, for instance, we have evidence that seems to show that sulphur in several forms is capable of oxidation in the body, as the administration of these substances always raises the acidity of the urine (see fig. 11).

The average acidity is about 2·5 grs. per hour or 60 grs. a day.

The highest acidity is at 6, 10, and 11 p.m., when it touches 4 grs. per hour; and the lowest at 9 a.m., when it is but little above 1 gr. per hour.

The acidity changes determine, as we have seen, the excretion of uric acid, which is high above urea when acidity is low, and below or close to urea when the acidity is high, and the amount retained each day when it is below urea, furnishes the excess excreted next morning when it is above urea; so that any unusually large retention on the evening of one day is followed, other things equal, by an unusually large excretion on the morning of the next day.

Thus the quantity excreted from 8 a.m. to 2 p.m. in this figure is partly the result of the low acidity which aids its solution, and partly also the result of the uric acid retained on the previous evening which furnishes the supply to be dissolved; and the amount by which uric acid will exceed urea on any given morning depends chiefly on these two factors.

The average excretion of urea is about 16 grs. per hour, or 384 grs. per day, and it fluctuates from a maximum of about 25 grs. per hour to a minimum of about 13 grs. per hour at 9 a.m. It appears to rise soon after each meal and to fall very decidedly in the early morning hours when the food supplies are running short, and this is no doubt the cause of the low acidity in these same hours.

The uric acid on this day bears a relation to urea of 1 to 32, which is not far off normal if the uric acid is provided both by formation and introduction, but if it had been provided by formation alone it would have been nearer 1 to 40.

The average excretion of water is about 75 cc. per hour, or about 1,800 cc. per day, but it varies enormously from a maximum of 230 cc. per hour between 11 p.m. and 1.40 a.m., and a minimum of about 33 cc. at 9 a.m.

The water is remarkably low all through the morning hours and up to 3 or 4 p.m., and this in spite of the fact that more than a pint of fluid is always taken with breakfast.

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No doubt this low water is partly due to loss of water by diuresis in the previous evening and night; but it is also more largely due to water being retained in the body and blood owing to the renal capillaries being obstructed by the excess of uric acid.

Similarly the remarkable rises of water in the evening and night are due to the presence of an excess of water in the blood, where it has been accumulating during the morning hours, and also to the freedom of the renal capillaries when the blood is cleared of uric acid; and with regard to the great diuresis of the night the uric acid is further below urea in these hours and those just preceding them than at any other time of the twenty-four hours.

We see then that my law of excretions is fully illustrated, and the more minutely we investigate it the better does it show that the urinary water is inversely as the uric acid and especially inversely as the height of the uric acid above urea.

And we have seen that the height of the uric acid above urea is the measure of the quantity of uric acid that is passing through the blood in any given hour.

It may be said that the water is scanty in the morning because there is none available, and that the blood is poor in water, but it is very easy to disprove this suggestion; first of all examine the blood and you will find that it is dilute, *i.e.*, both cells and hæmoglobin are relatively scanty in a given quantity.

Then having done this say at 9 a.m., give a drug which will bring down the uric acid, such as opium, calomel, or many others of which we shall have to speak very soon, and as soon as you have brought down the uric acid to or below the urea, you will get a diuresis perhaps as large as that at 7 p.m. Some of my results in this way have been very striking, and have proved absolutely that the urine in these hours was not scanty from want of water in the blood.

Control the uric acid and you will in all cases control the water; it matters not whether you bring down uric acid by raising the acidity, or by giving a drug such as one of the metals which directly forms an insoluble compound with it, if the uric acid comes down the water will go up, provided there is water available for excretion.

Conversely if you raise the uric acid by giving a solvent the water will come down, and will not rise again till the uric acid comes down, but we shall see numerous instances of all these things further on.

Again in disease the same law holds. Thus the onset of fever is

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accompanied by a rise of urea and acidity, and with this uric acid falls and is retained, and there is a more or less marked diuresis. I nearly always know when my temperature rises by the diuresis which marks its onset.

Still more is this the case when fever supervenes upon dropsy, for then there is a large supply of water available for diuresis, and if the fever continues this will last for several days till many pounds of water have been run off, and this proves conclusively that the scanty urine which often follows the onset of a fever is due to want of supplies of water and not to obstructed capillaries.

Conversely when the fever comes to an end the urea and acidity fall, and then the uric acid which has been held back during the early stages of the fever is again got into solution and passed through the blood, and with this we get a scanty excretion of water in spite of there being plenty in the blood.

Here we have the exact parallel in pathology of what occurs every day in physiology, the uric acid held back during the high acidity of the fever passes out when the acidity falls at the end of it, just as the uric acid retained in the evening and night when the acidity is high passes out next morning when the acidity is low.

And the diurnal variations in blood pressure, as also those which correspond to fever and convalescence, are as we shall see absolutely dependent on the uric acid.

Chronic Bright's disease gives us another illustration of the same thing. Here during the day hours there is severe uricacidæmia with obstructed capillaries and high blood pressure, and in spite of the ingestion of, it may be, large quantities of water, the urine is scanty but the blood is dilute. Such urine may have quite a good sp. gr., and the fact that it is the product of chronic Bright's disease may thus be overlooked.

In the night, however, this is reversed, there is a rise of acidity with lessened uricacidæmia and comparatively free capillaries, and with this goes so great a diuresis that the urine of the whole twenty-four hours is rendered profuse and of low specific gravity, and under these conditions the hourly excretion of water at night is often twice as large, or more than twice as large, as that in the day.

Before leaving fig. 3 I will just point out one of the ways in which it may be misread and give rise to misunderstanding.

Taking the law that urinary water is inversely as the height of the uric acid above urea. Suppose we take three hours, such as 7, 8 and 9 p.m., and mix the urines together, and suppose that the uric acid as at 8 and 9 was not only above urea but was rather higher

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above urea than in this figure, the mixing of these urines together might give a result showing a considerable excretion of water more than in several of the morning hours, and yet uric acid might come out above urea. Now anyone coming upon such a result would at once say "here is an exception to your law," but when you separate the hours carefully you see that the diuresis really occurred when uric acid was below urea, and in the following hours when it was above it the water was scanty, but the diuresis of the first hour was so great that it made the urine of the whole three hours seem profuse. There is no exception to my law, on the contrary, the more carefully it is investigated the more clearly does its truth stand out.

Conversely when there is no water there can be no diuresis, however much the uric acid is brought down, and the capillaries freed, if the water has been run off by perspiration, vomiting, or diarrhœa there will be no diuresis till fresh supplies have been introduced.

I do not claim that fig. 3 represents an absolutely typical day, it is one of many days taken more or less at random out of my researches, and many details do vary greatly from day to day with diet, clothing, temperature, exercise, and other things; but the main points that uric acid is above urea in certain hours and below it in certain others, that acidity is high in certain hours and low in others, and that the water varies inversely as the height of uric acid above urea, are practically constant both for my excretions and those of everyone living under similar conditions; and they are constant not only in physiology but for the most part also in pathology, and dominate, as we shall see, the circulation and consequently the nutrition and function of the whole body, and that probably from development and intra-uterine life up to the hour of death.

There is one further point of interest I will just mention in connection with fig. 3, and that is that when, as here, the urinary water is scanty in the morning hours from obstructed capillaries and not from want of water in the blood, there is an absolute distaste for fluids of all kinds, so that it is quite difficult to get them down; on the other hand, after a diuresis when the blood is poor in water there is thirst and a strong desire for fluids, so that by careful observation it is possible to tell whether in any given case the scanty urine is due to uricacidæmia and obstructed capillaries, or to want of water in the blood.

In the morning hours the drinking of a very considerable amount of water will not produce a diuresis, it is kept in the blood by the obstructed capillaries; in the evening and night it tends to pass very

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soon after it is swallowed, and precisely the same will occur in the morning hours if you bring down the uric acid and free the capillaries. No doubt water is required for digestion, and while it is active a certain amount of water will be retained for its purposes, but digestion takes place both in the morning and in the evening, and yet the water is profuse in the one and scanty in the other; and if you have removed the uric acid so that there is no plus excretion in the morning, the water will be passed freely then just as at other times, and under these circumstances there will be no great diuresis the following evening or night, because water has not been retained during the day.

It will have been noted that the afternoon alkaline tide is but poorly represented in fig. 3 by a small fall of acidity at 5 p.m., but this is one of the things that varies with exercise, food, and other factors, and I believe that the fall is commonly due to the alkaline bases introduced with lunch, aided by a certain amount of exercise commonly taken after lunch which tends to reduce the acidity by loss of acids in perspiration (see 3.45 and 4.45 in fig. 1); but in the day represented in fig. 3 there was no exercise after lunch because it was a pouring wet day and I did not go out.

The diurnal variations in the excretion of uric acid explain absolutely the times of incidence of the diseases which are due to it.

Thus of the diseases which are due to excess of uric acid in the blood, headache, epilepsy, mental depression, or melancholia and suicide, high blood pressure, angina, asthma, Raynaud's disease, all tend to come on or to be at their worst in the morning hours, though once there is any severe disturbance of digestion there may be uricacidæmia right through the day because the natural curve of acidity is upset.

On the other hand those diseases which are due to the presence of uric acid outside the blood, as gout and rheumatism, affect especially those hours in which the blood is generally cleared of uric acid, *i.e.*, the evening and night, and illustrations of all these points will be found in the chapters that treat of each disease.

The common diurnal fluctuations in the blood decimal correspond very well with those of acidity and uric acid in fig. 3, thus it is low in the morning with low acidity and high uric acid and rises towards 1 or 2 p.m. as acidity rises and uric acid comes down, then it falls more or less decidedly with the fall of acidity in the afternoon alkaline tide, varying with the distribution of meals and other factors, and rises very decidedly in the evening and early night

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hours. It will be noted that the curves in fig. 45 only illustrate some of these points, but this is a somewhat exceptional curve both as to uric acid and the blood decimal and it is given for reasons which appear in its description.

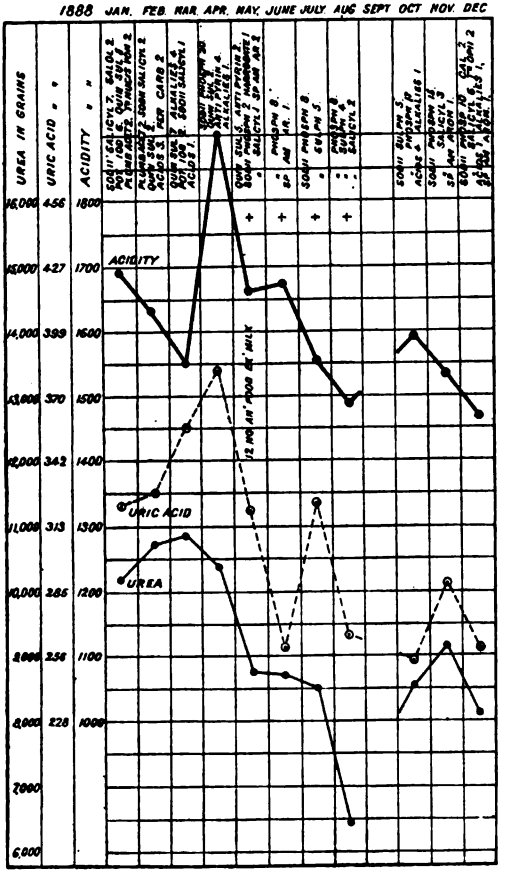

FIG. 4.—YEARLY EXCRETION OF URIC ACID FROM MONTH TO MONTH.

Fig. 4 is an attempt to show the annual fluctuations in the excretion of uric acid. I have no curves which show them well, because in the course of each year over which my investigation has extended, I have taken so many drugs that the natural fluctuations have always been more or less clouded over by their effects, and I have selected the year shown in the figure simply because it seemed to be less obscured by drugs than the others.

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What we see I think in this figure is that, speaking generally, the warm months of the year correspond to the morning hours of the day and show a relatively large excretion of uric acid, and it follows from our first principles that they should do this, for acidity is diminished in them all by an increased loss of acids from the skin in perspiration; conversely the cold months of the year correspond to the evening and night hours, as in them the acidity is raised by a diminished loss of acids from the skin, and with this we see a diminished excretion of uric acid.

Now in the cold months, October, November, December, January, and February, uric acid is nearer urea than at any other time, with the exception of June, of which I shall speak again.

With the fall of acidity in March uric acid rises.

The high acidity in April, May, June, July and August is due to the drugs taken, and the numbers opposite these indicate the number of days on which they were taken.

May, June, July and August marked + were not estimated throughout, but the excretion for the month was estimated from the days that were worked out.

In many months a considerable quantity of phosphate of soda was taken, and sometimes salicylate of soda also, and these would both tend to raise the acidity and also the excretion of uric acid, because they are solvents of uric acid.

In fact this year is selected not because few drugs are used but rather because they are used so constantly throughout the year that their effects may to some extent be neglected.

But whether we pay much attention to this figure or not the fact, I think, remains, that the acidity tends to be high in the cold months and low in the warm, and the uric acid in its inverse relation to this tends to be low in the cold months and high in the warm. It follows also from our diurnal experiences that uric acid will tend to be highest in the early warm months, March, April and May (and this may account for part of its fall in June, unless, indeed, June was a very cold month in 1888, which my notes do not enable me to say), and lowest at the first onset of cold as in October.

The fall of urea from March to May was due to my leaving off meat, of which I had previously taken a small quantity, and the further fall May to August was due to my making milk my only animal food without taking care to take sufficient milk and bread stuffs to replace the nitrogen left out, and this is an experiment which I do not advise anyone to repeat, and if I had known then what I know now about the direct introduction of uric acid, it would

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never have been necessary for me to do it; but I then believed that my only way of reducing uric acid was to reduce the total nitrogen.

Taking it that these are the natural annual variations in the excretion of uric acid, and the whole of my researches and observations are in favour of this, as I found out long ago that I got a relatively increased excretion of uric acid 1 to 29, or 1 to 30 in the spring and summer months, as compared with 1 to 33 in the winter, it follows that the greatness of the uric acid excretion in the warm months will, just as in the corresponding diurnal variations, depend partly on the greatness of the fall in acidity and partly on the quantity of uric acid which has been stored in the body in the previous cold months; and it is obvious that a man who has been introducing all through the winter some 6 grs. of uric acid per day, ought to suffer much more severely from such spring and summer diseases as are due to excess of uric acid in the blood, than the man who only introduces from 1 to 2 grs. per day, and evidence will, I think, not be wanting that this is the case; for the man who introduces 6 grs. a day not only introduces it, but the uric acid so taken interferes with its own excretion by tending to keep up the acidity of the urine and diminish the alkalinity of the blood, though it is true that if he goes on introducing it in summer it will tend to keep up the acidity then also; this, however, will have little effect compared to the external temperature, and whenever the acidity is reduced he will have a correspondingly great rush of urates into his blood.

We shall see also that all the diseases which in the diurnal variation of excretion tend to have their greatest incidence and severity in the morning hours, tend also to have their greatest annual incidence in the spring and summer months, while those which are most prominent in the evening and night will also be seen to be most prominent in autumn and winter, and I must add on to the diseases which are worse in the morning hours, some others, such as phthisis, skin diseases, and pneumonia, because they are not of such a nature as to show well their relation to the diurnal fluctuations of uric acid, but yet as we shall see some of them do show very well a distinct relation to its annual fluctuations.

It will no doubt be a surprise to some to see such diseases as phthisis and pneumonia included in the list; but we shall see in chapter iv. and elsewhere, that uric acid, by controlling the metabolism and combustion of the body, does in very many instances absolutely determine whether microbes shall be burnt up and destroyed, or obtain a footing and live within it, and in this

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way does practically determine both the incidence and course of microbic diseases. Moreover, we shall also see (chapters ix. and xvii.) that uric acid by affecting the fibrous tissues of the trachea and bronchi not only produces acute inflammation of these structures, but also brings about pneumonia of neighbouring portions of the lungs, and that in any of the lesions so produced, bacilli and other microbes may find a nidus.

Fig. 5 shows, I think, that the diurnal variations in the excretion of uric acid have a not unimportant effect on the temperature of the body.

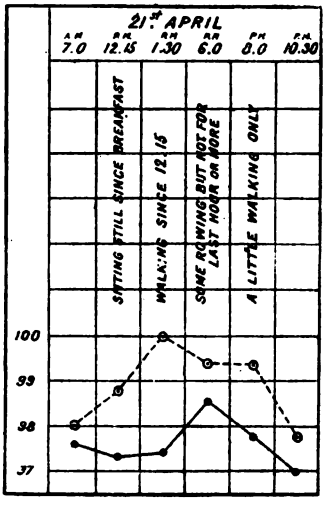

FIG. 5.—CURVES OF TEMPERATURES IN MOUTH AND RECTUM TO SHOW THEIR RELATION TO THE EXCRETION OF URIC ACID.

This figure is one of a large number which I have, and which all show much the same thing, and I give it here while the diurnal variations in the excretion of uric acid are fresh in our minds, though I shall have to return to its points in connection with other subjects later on.

The upper curve gives the temperature in the rectum, the lower curve that in the mouth.

And what we cannot help noticing at first sight, is that between the hours of 7 a.m. and 6 p.m. these temperatures are further apart than at other times of the day.

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I was led to investigate this matter by some statements I found in Marey's work on the circulation of the blood ("Circulation du Sang," pp. 588 to 596).

As he points out that by observing the temperature simultaneously in the rectum and the mouth we can tell whether a low temperature in the mouth is due (1) to contraction of surface vessels, or (2) to diminished production of temperature.

If it is due to contraction of surface vessels, the rectal temperature rises as the mouth temperature falls, and the temperature of the two places are far apart; on the other hand, if it is due to diminished production of heat, the temperatures in the two places will be close together.

Again, suppose we find a raised temperature in the rectum, if the temperature in the mouth is nearly the same, there is an increased formation of heat, but if they are far apart, the mouth being lower, there is contraction of skin vessels.

Marey also points out that in cholera algide the rectal temperature is high in proportion as the surface temperature is low, and in the reaction the rectal temperature falls as the surface temperature rises.

In cholera algide the surface vessels are contracted, and tartarate of antimony and emetine both produce similar results.

Alcohol, on the other hand, dilates the surface vessels and reduces the temperature in the rectum.

Inanition lowers the temperature both of surface and rectum, hence the diagnosis between this and contracted arterioles, or rather obstructed capillaries (see chapter v.).

In uræmia he points out that you may get a fall of the central temperature as well as that of the surface, *i.e.*, I suppose that the obstruction of vessels is so great and general that the production of heat is affected as well as its distribution.

During fever the two curves come together as the vessels are dilated, and the temperature equalised everywhere.

In cases of intermittent fever the curves are close together at the times of high fever, but the surface temperature is considerably the lower in the intervals, and this corresponds, as I know, pretty absolutely with the amount of uric acid in the blood, as it is absent during the fever, being stored up in the enlarging spleen, in the liver and elsewhere, and present in more or less considerable quantity during the intervals.

These observations could not but suggest to my mind that if the difference between the temperature of the mouth and rectum is a

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measure of the obstruction of the skin vessels, it might also be a measure of the amount of uric acid in the blood, for uric acid in the blood obstructs the skin vessels; and on carefully investigating the point I found, as fig. 5 shows, that this is the case; and that the greatest divergence of these temperatures corresponds exactly with those hours of the day in which there is naturally the largest amount of uric acid passing through the blood.

In this figure we see that at 7 a.m. the two curves are pretty close together, and this temperature was taken in bed, so that any effect that uric acid might have on the skin vessels was counteracted by the equable temperature of the bed clothes, and this is practically a constant feature day after day.

The next observation is at 12.15 p.m., and here we see that the mouth temperature has fallen, while the rectal temperature has risen, so that they are considerably further apart than at 7 a.m., and the skin vessels are therefore obstructed.

At 1.30 p.m. the mouth temperature has risen very slightly, but the rectal temperature has risen considerably, and they are now 2½ degrees apart.

An hour and a quarter of walking exercise has been taken, and has, as is usually the case, raised the temperature, but it has affected the rectal temperature much more than that in the mouth, as the surface vessels are still obstructed.

At 6 p.m. the mouth temperature has risen very decidedly and reached its highest point, the rectal temperature has fallen and come to meet it, and they are now only separated by about $\frac{8}{10}$ of a degree, the surface vessels are therefore but little obstructed, and the alkaline tide, with the uricacidæmia that accompanied it, has come to an end.

At 8 p.m. the rectal temperature remains the same as at 6, while the mouth temperature has fallen. They are about 1½ degrees apart, and the surface vessels are again a little obstructed; possibly there was again a slight excess of uric acid passing through the blood, as there was at 8 and 9 p.m. in fig. 3, but at 10.30 p.m. this has come to an end, the mouth temperature has fallen to its lowest point, but the rectal temperature has fallen still more and is now again pretty close to it; the skin vessels are but little obstructed, and the blood, as we know, is probably pretty clear of uric acid.

I have many curves showing almost exactly the same thing, and when there is no exercise to cause fluctuations the greatest divergence of temperature always occurs about 1 p.m., and they come together again early in the afternoon, and remain more or less close together in the evening and night.

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The effect of exercise is very interesting, for it causes divergence of the two curves most in the morning, but to a considerable extent also in the afternoon, and as we shall see further on, exercise increases the excretion of uric acid and causes an increased quantity of it to pass through the blood; we shall also see that in accordance with its effects on uric acid, exercise controls the formation and excretion of urea; its effects on these temperature curves show that it controls the distribution of heat, and we shall see reason to believe later on that it also controls its formation.

In the same way uricacidæmia will account for the algide stage of cholera, as uricacidæmia is the natural and constant result of every severe gastro-intestinal disturbance. Tartarate of antimony or emetine act in the same way and produce the same result, and sea sickness as I know, also does the same.

Alcohol on the other hand, or the acids so often mixed with it, cures or prevents uricacidæmia, and consequently allows the skin vessels to relax and the temperature curves to come together, and I believe that every drug which has the same effect on uric acid has also the same effect on the curves.

In uræmia, which I have long been pointing out is merely severe uricacidæmia, the obstruction of vessels may be so great that there is diminished production of heat, just as we shall see that in severe fatigue there is diminished production of urea.

If the effect of uric acid is so great in the physiological conditions which obtain in fig. 5, its effects in pathological conditions must often be much greater, and so far as my observations go this is certainly the case.

It is obvious also, that in observing in this way the superficial and deep temperatures and their relations to each other, we have at hand a ready means of estimating the amount of uric acid that is passing through the blood at a time when it might be quite impossible to estimate directly the quantity either in the blood or the urine, and we can control our results by the use of drugs which are known to influence the solubility of uric acid, and which will therefore affect the temperatures.

We have thus three distinct means by which we can gauge the amount of uric acid passing through the blood. (1) We can examine the blood decimal itself; (2) we can take the rate of the pulse and the size of the radial artery with the arteriometer: the pulse being slower and the size of the radial diameter greater the more the uric acid in the blood; and lastly we can take (3) the relation to each other of the temperatures in the mouth and rectum of which I

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have just been speaking. And all these things will be found to vary in the most definite relation to the excretion of uric acid in the urine as we shall see with regard to the blood in figs. 45 and 65 and elsewhere, and indeed the correspondence between the conditions of these two fluids is often so exact that where absolute quantities are not required the one may be inferred from the other.

We are now in a position to consider the action of drugs. So far as we have gone, we see that the hourly, daily, monthly, and yearly excretion of uric acid has to do with the variations produced by introduction on the one hand, and the effects of various factors on solubility on the other, while there is no proof whatever that the formation of uric acid relatively to urea ever alters at all.

In the same way with drugs we shall see that they act merely by increasing or diminishing solubility and influence excretion accordingly, but there is no evidence that any of them can produce an increased formation of uric acid; and what has been said by others to be due to increased formation of uric acid has, I believe, always been due either to increased introduction in food substances, or to increased elimination from the action of solvents.

I myself found out very early in my investigations that by influencing the solubility of uric acid I could do almost anything I liked with its excretion; and more recently, that by controlling the amount introduced into the body, I could exercise still further and more decided control over the amount that could pass into and through the blood (see fig. 64).

And when we once fully recognise the enormous power which uric acid has in controlling the circulation, we shall see that this knowledge gives us a lever of the utmost importance in guiding both the physiology and pathology of the human body, and a power of explaining almost numberless facts and sequences in both regions which are otherwise inexplicable.

And now in speaking of the action of drugs I shall divide them into (1) those that increase, and (2) those that decrease excretion, and having first enumerated those in each class, shall say a few words as to the action of the individual drugs in turn.

The chief substances which increase the excretion of uric acid are alkalies, salicylic acid and its compounds, salicin, salol, &c., phosphate of soda, piperazidin, quinine and belladonna.

I place alkalies first because they are found in action every day in nature, and hence have far greater importance than any substances which are not in every-day action. The curves in fig. 6 show the effects of giving the alkaline salts of potash and soda.

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We see that they produce a decided fall in the acidity curve in day 2, and keep it more or less low on days 3 and 4. The result of this is that uric acid, which is close to urea on day 1, rises considerably above it on day 2 and remains high on day 3, and is still fully half a grain above it on day 4. The rise of urea on day 2 is not the result of taking the potash, but of some alteration in diet or exercise; other things equal a fall of acidity and a rise of uric acid tend to depress urea.

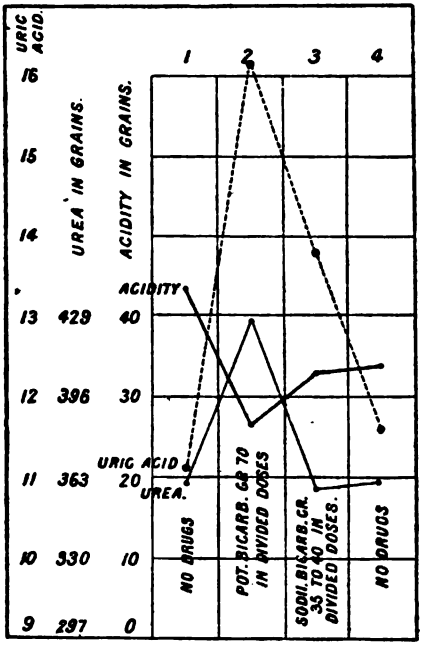

FIG. 6.—PLUS EXCRETION OF URIC ACID PRODUCED BY ALKALIES.

Speaking generally, and apart from the action of other solvents, it seems as I have said that the excretion of uric acid from day to day and hour to hour is inversely as the acidity of the urine.

And I think there is evidence to show that, speaking generally, the fluctuations in the acidity of the urine correspond both in direction and extent with fluctuations in the alkalinity of the blood; thus it has been shown by Peiper (Virchow's "Archives," June, 1889, p. 337) and others, that the alkalinity of the blood is diminished in all fevers except such as are complicated by dyspnœa

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and cyanosis, and the acidity of the urine is increased in all fevers; a good instance of this fact being recorded in Sir W. Roberts' work "On Urinary and Renal Diseases," fourth edition (p. 59), where a patient with alkaline urine got erysipelas, and the urine became acid and remained so during the fever, becoming alkaline again at the end of it (see previous remarks on fig. 5).

Conversely a vegetarian diet is known to diminish the acidity of the urine, and I believe that it also increases the alkalinity of the blood. There is, however, one exception to the above statement about the relation of the excretion of uric acid to the acidity of the urine looked upon as an index of the alkalinity of the blood; and that is where, as in the fits of epilepsy (see cases in chapter vii.), there is a huge excretion of uric acid relatively to urea; for here the acidity of the urine is extremely high, and the greater the amount of uric acid present the higher the acidity. It thus appears that when a very large amount of uric acid is being excreted the acidity of the urine is no safe index of the alkalinity of the blood, because the acidity of the excretion is directly affected by the amount of uric acid it contains.

But it is usually easy to distinguish this pathological exception to the rule, for the usual relation between acidity and urea no longer holds good. In the urine excreted after a fit acidity rises, but urea is steady or even falls a little (see chapter vii.), the rise of acidity is therefore not due to the ordinary urea metabolism, but it corresponds with a very marked rise in uric acid, and may, I think, be due to this; the alkalinity of the blood on the other hand varies inversely with the metabolism of urea, and is therefore high and rising. A similar rise of acidity, not accompanied by any rise of urea, is seen in several of the figures, showing the effects of taking uric acid or xanthin compounds (figs. 24 and 25).

Sir A. Garrod has shown that the alkalies soda and potash form extremely soluble compounds with uric acid, and phosphate of soda is also well known as a solvent of uric acid. Fig. 7 shows its effects; here in day 1 uric acid was far below urea owing to the high acidity, which again was due to the taking of acids and antipyrin. A drachm of phosphate of soda is taken three times on day 2, and uric acid rises and gets just above urea, which has fallen.

Now this high urea on day 1 was probably partly due to the low uric acid, because, as we shall see in chapter viii. and elsewhere, everything that brings down uric acid tends to raise urea, or in other words, the clearing the blood of uric acid quickens the metabolism

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throughout the body, and stimulates the formation and excretion of urea; but this only lasts for a short time, therefore urea does not remain up on day 2.

On day 3 a similar dose of phosphate is taken, and uric acid rises more decidedly above urea, and on day 4, when the drug is left off, but no other change is made, it falls a long way below it.

We see then that phosphate of soda causes a distinctly increased excretion of uric acid, which, just as in the case of some other solvents, is followed by a fall when the drug is left off; proving, I

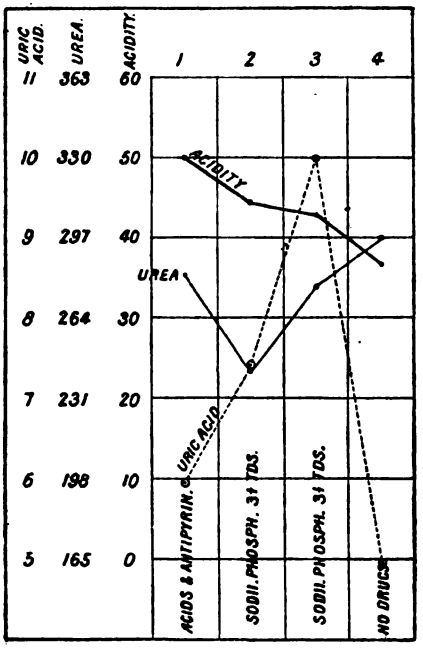

FIG. 7.—PLUS EXCRETION OF URIC ACID PRODUCED BY PHOSPHATE OF SODIUM.

think, that we are dealing with excretion merely, and not with any new formation of uric acid.

As to salicylic acid and its compounds, I have shown that they increase the excretion of uric acid, and I have pointed out that what is known about the compound (salicyluric acid) which they form, seems to show that it is not only more soluble in water than the salts of uric acid, but also much more soluble in slightly acid fluids —a very important point to which I shall often have to refer again.

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I should perhaps explain with regard to salicyluric acid that it is not a compound of uric acid and salicylic acid, but of glycocoll, one of the constituents of uric acid and salicylic acid; just as hippuric acid is a compound of glycocoll and benzoic acid.

And what I say with regard to the solubility of salicyluric acid applies to its presence in the blood only, for where it is present in the urine it does not give any reaction with Haycraft's process, and is therefore, so far as my results are concerned, not estimated as uric acid. So that in so far as a salicylate increases the excretion of uric acid, the compound salicyluric acid, which it may form with it in the blood is probably largely reconverted into uric acid and salicylic acid as it passes the kidney (see my experiments with regard to these points in the *Transactions of the Royal Medical and Chirurgical Society*, vol. 71, p. 137).

I regret also that the statements regarding the solubility of salicyluric acid to be found in standard works of reference on chemistry are not sufficiently definite for our purpose, so that we have to be satisfied with probability rather than with certainty.

But if this somewhat hypothetical chemistry serves in the meanwhile to remind us of the clinical fact, that salicylates are not good solvents of uric acid when the alkalinity of the blood is high and the acidity of the urine low, and that for the same reason it is a mistake to give alkaline salts of sodium or potassium along with them (see fig. 62 and cases narrated in chapters ix. and xvi.), it will not be entirely useless.

Fig. 8 shows the effect of a salicylate on excretion, and I need hardly describe it at great length. It shows a great plus excretion on day 2, the first under the salicylate salt, followed by a fall next day, the same dose being continued; and a second rise on days 4 and 5, a fall on day 6, and a great fall on day 7, when the drug had been left off. This last is a constant feature of the exhibition of a salicylate, and as will be seen further on, I have made use of it for studying the effects of absence of uric acid from the blood, both in physiology and pathology (chapters viii. and xii.). I think that most of the available uric acid was cleared out by the solvent on day 2, hence the fall on day 3, and that the rise on days 4 and 5 was due to some fresh introduction of uric acid with the food. This figure unfortunately does not give the water or it would have been low on day 2, followed by more or less diuresis on day 3, for here as elsewhere the water is inversely as the uric acid, and this explains the observation made by others that the diuresis produced by salicylates does not come till the second or third day of their

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action, and this depends on the amount of available uric acid, when this is large it will remain high for several days and the diuresis will not come till it falls. This figure, and all the curves of excretion under salicylates show, I think, that we have to do with excretion and not with formation of uric acid; if salicylates cause new formation of uric acid, why does the curve never again reach

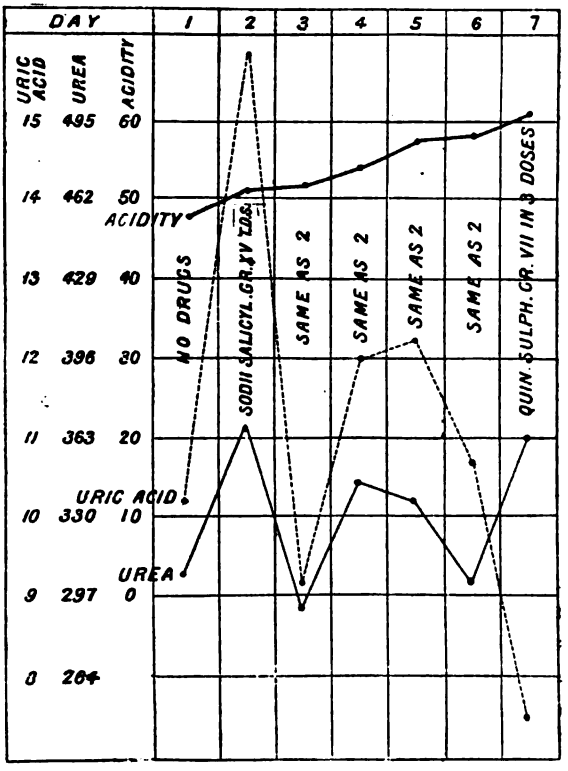

FIG. 8.—PLUS EXCRETION OF URIC ACID PRODUCED BY SALICYLATE OF SODIUM.

the height attained on the first or second day though the drug is continued as before?

I have further shown that as regards acute rheumatism the salicyl compounds are powerful in curing the disease exactly in proportion to their power of eliminating uric acid; that, dose for dose, salicylates are most powerful in both respects, and are followed by salol, and at some distance by salicin. I shall also have to point

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out in chapter xvi. that when the natural solvent action of salicylates is prevented (see previous remarks about salicyluric acid), they then send up the temperature and greatly increase the pains of rheumatism in place of their usual satisfactory action, so that there is no doubt whatever that these salts cure acute rheumatism just as alkalies (soda and potash) did before them, by dissolving and eliminating uric acid, and that the fever and pain of this terrible disease are entirely due to the irritation of fibrous tissues which uric acid produces.

Phosphate of soda, the ordinary Na_2HPO_4, is a good solvent of uric acid, and causes a plus excretion, but unlike the salicylates, it can only act in an alkaline medium, or while the supply of alkalies is abundant; the presence of any acid, or even of a salt of a mineral acid as a sulphate, appears to convert it into the acid phosphate NaH_2PO_4, and then there is no longer a plus excretion of uric acid.

The practical point to remember, then, is that phosphate of soda should be given with alkalies, or in conditions when the supply of alkalies in the blood and tissue fluids is good, and it will then cause a satisfactory plus excretion of uric acid, as in headache, high tension pulse, and mental depression, when the alkalinity is high. Salicylates, on the other hand, act best when the alkalinity of the blood is low, and their action as regards the excretion of uric acid appears to be absolutely hindered by the presence of alkali, so that they do best in conditions of fever when the alkalinity is generally low, and in conditions where there is little or no fever, it may be necessary to give them with opium or ammonia which raise the acidity, or in alternate doses with acids to obtain their full effect on the excretion of uric acid, and not a few failures in the practical treatment of disease with salicylates are, I believe, due to ignorance of these facts.

I have made a few experiments with piperazidin, and it appears to increase the excretion of urates, but it is certainly not a very powerful excretant, and cannot compare with salicylates, for instance, unlike salicylates also its action is interfered with by acids; thus, when the hydrochlorate of piperazadin is taken the first effect of a dose of 12 to 15 grs. is a minus excretion of urate and diuresis, followed later by some plus excretion, which, however, lasts for some time.

Belladonna is a drug which has interested me very greatly, chiefly because its action is so absolutely the reverse of that of opium.

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Now, opium relaxes the arterioles, lowers the blood pressure, quickens the heart, improves the circulation in the skin, and raises its temperature (see remarks on fig. 5), increases the urine, and causes mental brilliancy and well being. Belladonna, on the other hand, constricts the arterioles, raises the blood pressure, slows the heart, diminishes the circulation in the skin and lowers its temperature, diminishes the urine, and causes mental dulness and tendency to headache.

Now, I pointed out some years ago in the *British Medical Journal* (1889, vol. 2), in a paper on "The Influence of Opium and

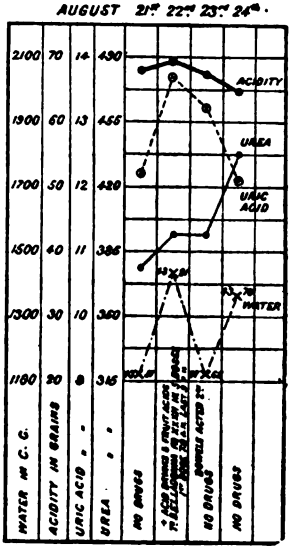

FIG. 9.—PLUS EXCRETION OF URIC ACID PRODUCED BY BELLADONNA.

Morphine on Uric Acid considered with Reference to their Action in Health and Disease," that opium owes the whole of its activity as above mentioned to its effects on the solubility and excretion of uric acid, that the whole of its above effects are due to its clearing the blood of uric acid, which again is due to its raising the acidity, which again is due to its slowing down peristalsis, and thus increasing the absorption of nitrogenous and acid substances from the intestines, especially the large intestine.

And we shall see, I think, presently, the full interest and bearing my remarks when I point out that belladonna owes its absolute

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antagonism to opium in the above matters to its absolutely reverse effects on the solubility and excretion of uric acid, which again is due to its lowering the acidity while opium raises it, and this in turn is due to the fact that belladonna increases peristalsis and diminishes the absorption of nitrogen and acid substances from the intestines, the exact reverse of the effects of opium.

Fig. 9 shows the effects of taking ℥xxxii. of tincture of belladonna in divided doses between the hours of 7 a.m. and 9 p.m. on August 22.

The effect we see at once is a pretty decided rise of uric acid, which drops a little on the 23rd, and still more on 24th, coming below urea.

The effect of belladonna on peristalsis is shown by the fact that the bowels, usually extremely regular, acted twice on the 23rd.

The effect on acidity is not so clear, because unfortunately on the 22nd, some extraneous force raised the urea, and the dryness of the mouth was so great that a considerable quantity of acid drinks were taken; on the 23rd and 24th, however, there was a pretty decided fall in spite of the fact that urea was still rising, and on the 23rd there was a break in the upward movement of the urea corresponding no doubt with the increased action of the bowels on this day.

It will of course be said that belladonna did not diminish the urine, but I would point out that the rise on the 22nd was entirely due, as the figures show,[1] to the diuresis at night when no doubt the acids taken produced their full effect and relaxed the arterioles a bit; in the day hours it was not more profuse than on the 21st, in spite of the increased quantity of fluid taken. And on the 23rd, when the acidity had fallen distinctly, and the uric acid was still high, the water in the day hours was very scanty.

On several occasions when taking atropine or belladonna, I have had very decidedly slow pulse—66 or below that, with all the signs of high blood pressure, and some threatening of headache.

Belladonna thus ranges itself along with the drugs which cause an increased excretion of uric acid, and many of its physiological effects are common to them all.

Quinine increases the excretion of uric acid in the urine, and I

[1] The figures to the left of the water curve represent the hourly excretion of water in sixteen hours of the day, that is, the total excretion of those hours divided by sixteen, similarly the figures to the right of the curve represent the hourly excretion of water in eight hours of the night.

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am inclined to believe that it does this by contracting the spleen, a well-known reservoir of uric acid.

Where the spleen is large, as in malaria, leucocythæmia, &c., and the excretion of uric acid is generally large, the exhibition of quinine very greatly increases it.

In fig. 10 we see the effects of giving quinine gr. vii. in twenty-four hours, and while the drug is continued there is a fairly steady and well-maintained rise in the excretion of uric acid which seems to pay but little attention to the fluctuations of acidity.

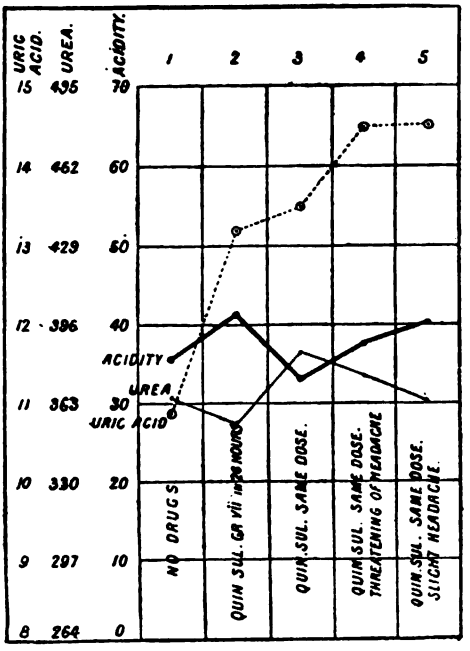

FIG. 10.—PLUS EXCRETION OF URIC ACID PRODUCED BY QUININE.

When I first noticed the increase of uric acid under quinine I thought that we had to do with a plus formation of uric acid which I had not otherwise met with, and therefore regarded with interest; but I found that when I gave a course of salicylate before the quinine (*i.e.*, removed all the available uric acid from the spleen) it was no longer able to cause a plus excretion, hence I concluded that I had to do with excretion and not with formation, both in normal conditions and where the spleen is enlarged (see the last day of fig. 8).

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When quinine squeezes the uric acid, as we are supposing, out of the spleen, it produces more or less uricacidæmia, and the signs of this blood condition are among the prominent symptoms of quinism. Thus, the headache which quinine produces in many people is well known. I have pointed out that quinine is said to do harm in epilepsy, or may even produce epilepsy; it is also recorded that quinine given in large doses for malaria may produce hæmoglobinuria (*Progrès Medicale*, July, 1888, p. 4), and for my arguments about this latter trouble see chapter xii.

I have several times met with patients with large spleens who objected strongly to taking quinine, as they said it always gave them a bad headache, and this is just what I should expect (see also *Brain*, Spring number, 1891, p. 73). And Dr. Lauder Brunton, in a most favourable mention of my work ("Cavendish Lecture," 1891, *Lancet*, vol. i., 1891, p. 1361), says that it enabled him to understand how a patient under his care with a very large spleen was able to keep on passing uratic gravel. Dr. Brunton had almost concluded that he must have a stone in his bladder, of which portions were being excreted, but after death no stone was found. No doubt this patient was passing a great excess of urate, having a relation to urea of 1—10 or 1—12, and some of this would, from time to time, from absence of pigment or salts or excess of acids, &c. (see Sir W. Roberts, *Medico-Chirurgical Transactions*, vol. lxxiii., p. 266), be deposited in the urinary passages, so that our knowledge of the formation and excretion of urates is likely to throw some light on the formation of calculi (see also *Lancet*, February, 1888, p. 1010, for a case in which there was a large spleen and a urate calculus was quickly formed).

Ranke and others state that quinine diminishes the uric acid in the urine, and this statement being diametrically opposed to my own results puzzled me for some time, but I now believe that it can be easily explained.

Sulphate of quinine has a double action on uric acid, that is to say, it has the action of a sulphate, which, as I shall show presently, causes retention of uric acid and clears it out of the blood, and then it has the action on the spleen, causing uricacidæmia and a plus excretion of uric acid.

If a small dose (6 grs. in twenty-four hours) of sulphate of quinine is taken and its effects are watched from hour to hour, what is seen is this: there is first of all a rise of acidity of urine, a minus excretion of uric acid, a relaxation of arterioles and a plus excretion of water (diuresis); later on acidity falls and uricacidæmia

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sets in; with this there is slower pulse, diminishing urinary water, and a tendency to headache, and generally with small doses the second stage of uricacidæmia and plus excretion outweighs the minus excretion of the first stage; but with large doses of sulphate —6 to 15 grs.—(and Ranke and others specially mention large doses), the effect of the sulphate would be more powerful and lasting, and the minus excretion of uric acid, with reduced arterial tension and diuresis, might continue a whole twenty-four hours or

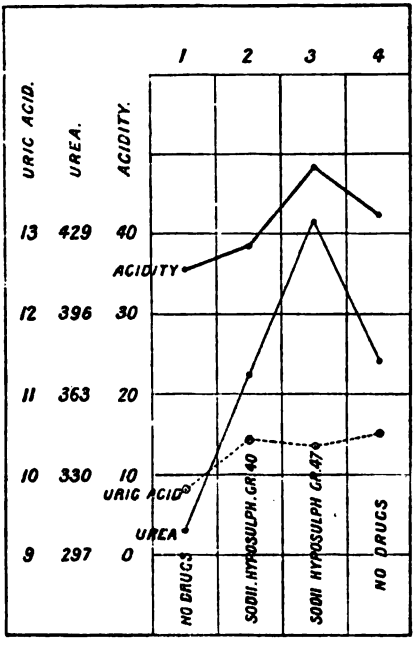

FIG. 11.—RETENTION OF URIC ACID PRODUCED BY ACIDS.

more, hence the difference between my results and those of others is due to difference of dose, and is apparent rather than real.

We must remember also that quinine is an alkaloid or xanthin, and that a certain proportion of the quantity swallowed is therefore equivalent to uric acid. Then if we take the chemical formula for acid sulphate of quinine and remove from it the elements of uric acid, these would bear a proportion to the entire acid sulphate of about 1 to 5, and several experiments I have made by taking known quantities of the sulphate and watching the corresponding

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increase in the excretion of uric acid, at a time when there was no introduction of uric acid, and as far as possible no other uric acid available for solution, have given results very close to this theoretical calculation.

Whether the xanthin element in quinine is sufficient to account for the whole increased excretion in fig. 10 is another matter; but there is little room for doubt that where quinine is given in very large doses as for malaria, much of the large excretion of uric acid which follows may be due to this introduction. Other vegetable alkaloids such as strychnia seem to give similar results, and increase the excretion of uric acid in proportion to the xanthin elements they contain.

The chief substances which diminish the excretion of uric acid are acids, iron, lead, mercury, silver, copper, zinc, and other metals, lithia, manganese, calcium chloride, and other salts of calcium, acid phosphate of soda, some sulphates, chlorides, &c., and many substances which directly or indirectly raise the acidity, or otherwise form insoluble compounds with uric acid, as opium, cocaine, the iodides, antipyrin, ammonium, the nitrites, some hyposulphites, and other compounds of sulphur, and many less well-known substances.

All these substances diminish the excretion of uric acid, and bring about its retention and accumulation in the body. They clear it out of the blood and produce the symptoms of its absence from the circulation, which are for the most part the reverse of those produced by its presence. They drive the urates out of the circulation into the joints and fibrous tissues, where its arrival may be evidenced by pricking and shooting pains (see gout), also into the liver, spleen, and other organs.

I place acids at the head of the list because their action dominates the physiology of every-day life, and their range of action is therefore infinitely more extensive than that of the other members of the list whose presence is more or less accidental and temporary. Fig. 11 shows us the effects of acids, or rather, of the rise of acidity produced by taking hyposulphite of sodium. Acidity rises moderately on day 2, more decidedly on day 3, and falls again on day 4, after the drug has been left off. Uric acid, which is above urea on day 1, gets decidedly below it on day 2, a long way below it on day 3, and is but a comparatively small distance below it on day 4, as acidity falls again.

Acidity of urine bears, as I have shown, a fairly constant relation to urea, both tending to rise and fall together, and the relation I

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have given, 1 of acidity (reckoned as oxalic acid) to 6·3 of urea, is very constant. Whatever (food, exercise, &c.) raises urea raises acidity, and *vice versâ;* thus a meal of mutton or beef will increase urea, and it has been suggested by some authors that the concomitant rise in acidity is due to the salts contained in the meat (Senator, *Ziemssen*, vol. xvi., pp. 126-7). Thus meat not only increases the formation of urate but interferes with its excretion and promotes retention, and we shall see presently, that it also introduces urate ready formed into the body. Then acids are contained in many articles of diet, and especially in wines, beers, and other drinks, cider, lemonade, &c. Sir A. Garrod, it may be remembered, attributed the gout-producing powers of beers and certain wines to some unfermented matters they contained, but I have shown (*British Medical Journal*, vol. ii., 1888, pp. 10-11), that the acids they all contain in very large quanity, and without which beers, for instance, would neither keep good nor be palatable, quite sufficiently account for their gout-producing powers. Acids, again, may be formed by certain fermentation processes in digestion, a question which M. Bouchard has very ably worked out (*Leçons sur les Auto-Intoxications*, p. 172).

Sir A. Garrod has shown (prev. ref., p. 258) that suppression of perspiration is immediately followed by a rise in the acidity of the urine, and I can prove that increase of perspiration diminishes the acidity of the urine (see also fig. 63). Hence we can explain how hot rooms or warm south-west winds diminish the acidity of the urine, increase the excretion of uric acid, and produce the feelings of langour and depression which are due to its presence in the circulation; also how a cold north-east wind raises the acidity and produces the reverse effect, making us cheerful and brisk.[1]

Last, but not least, deficient oxidation lowers acidity. I have previously mentioned that according to Peiper, fevers accompanied by dyspnœa and cyanosis form exceptions to the rule that fever raises the acidity of the urine and diminishes the alkalinity of the blood, and it seems to me that deficient oxidation must mean deficient formation of acids (see *St. Bartholomew's Hospital Reports*, vol. xxvi., p. 19 of my paper), hence the cause of the above exception to the rule.

I have very little doubt, therefore, that many of the headaches which people suffer from after theatres, church, and other meetings

[1] As to the fact that sweat at the time of its discharge from the ducts is normally acid, see *Heuss Monatschr. fur prakt Derm*, No. 9, 1892.

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are due to the heat and deficiency of oxygen, both of which lower the acidity of the urine, increase the alkalinity of the blood, and flood it with any uric acid that may be at hand ready to be got into solution; but as I have said before, if all the available uric acid has been previously removed, none of these conditions will have any effect, and a knowledge of these simple facts about uric acid enables me to explain hundreds of sequences in the physiology and

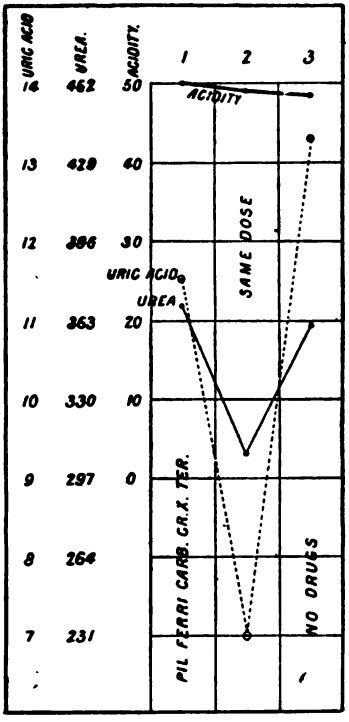

FIG. 12.—RETENTION OF URIC ACID PRODUCED BY IRON.

pathology of everyday life, of which I can only mention a very few here.

With regard to iron and lead, Sir A. Garrod has shown that these substances form insoluble urates, and they therefore fall at once within my rule, and diminish the excretion of uric acid because the compounds they form with it are insoluble, just as alkalies (potash and soda) phosphates and salicylates increase its excretion because they form soluble compounds with it.

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The first effects, then, of iron and lead are to diminish the excretion of uric acid and clear it out of the blood, and at this stage they produce on the one hand the symptoms which we shall presently see are due to its absence from the blood, and on the other they may produce the pricking and shooting pains which indicate its presence in joints and fibrous tissues.

Fig. 12 shows the effect of giving gr. x. of pil. ferri carb. three times a day. There is a very marked fall of uric acid on

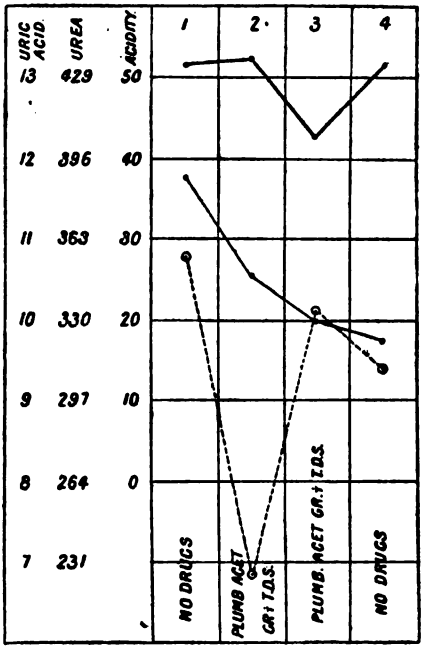

FIG. 13.—RETENTION OF URIC ACID PRODUCED BY LEAD.

the second day, followed by a rise—what I have called a rebound—on the third day, when no iron is taken. This large excretion on day 3 is the result of the increasing solubility of the blood, now that it contains less iron, and also of the diminished excretion or retention of uric acid in day 2, just as occurs in the normal physiological excretion of the alkaline tide of the morning hours. See remarks on figs. 1, 2 and 3.

Fig. 13 shows the effect of giving gr. 1 of acetate of lead three times a day for two days. Here the fall of uric acid comes on the

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first day the drug is taken, and there is no rise of acidity to account for it, so that it is the result of the insoluble compound which uric acid forms with lead.

But the fall does not continue; on the contrary, in spite of the lead being continued, uric acid is above urea next day. Acidity however, falls decidedly, and this is the cause of the rise of uric acid. This figure therefore proves that no drug which causes intestinal irritation can continue to cause diminished excretion of uric acid, no matter how insoluble may be the compound it forms with it. For the intestinal irritation causes a fall of urea and of acidity, and the uric acid passes into solution with the neutral phosphates of the blood and disregards, so to speak, the lead. We shall see that exactly the same thing occurs with mercury, copper, zinc, silver, or any other metal whose urate is insoluble, and the moment that they cause any intestinal irritation, or purgation, they cease to keep down the excretion of uric acid. This fact also is of enormous importance for the correct understanding of the physiology and pathology of uric acid, because it shows that everything, food, drink, drug or disease product, that causes in any way gastro-intestinal irritation, will produce a fall of urea and of the acidity of the urine, and a plus excretion of uric acid; in other words, it will flood the blood with uric acid, and the results of this uricacidæmia will promptly make themselves felt.

We have seen that the increase of peristalsis is the cause of the uricacidæmia, and so of many other effects which belladonna produces (fig. 9). We have yet to see that the diminished peristalsis of opium or morphine is the cause of their action in clearing the blood of uric acid, and so of many of their most important effects, and we shall meet with the same results of intestinal irritation in nearly all the diseases which are due to uric acid, especially those such as headache, epilepsy, mental depression, hæmoglobinuria, anæmia and Bright's disease, which are due to excess of uric acid in the blood; in these and many others dyspepsia and its effects in producing uricacidæmia are most deadly.

But to return to fig. 13: on day 3 the lead caused well marked intestinal pain and griping, this caused diminished appetite with deficient digestion and absorption, hence a fall of urea and acidity, and though the lead in the blood no doubt combined with some uric acid, the rising alkalinity dissolved a considerable quantity of that which was retained on day 2, and so there was no retention on day 3.

In this way iron or lead will produce or precipitate the arthritis

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of gout or rheumatism, but will clear up headache or mental depression due to uric acid in the blood.

But this is only the first stage of their action, and it is necessary to remember what has been said about the rebound, or great confusion as to cause and effect will result in the minds of observers.

Take lead again, for instance, as the history of plumbism is well known; its first effect is to store in the liver, spleen,[1] joints, and other fibrous tissues some 3—4 or more grains of uric acid; then it begins to cause intestinal irritation (possibly from a deposition of insoluble urate of lead in the fibrous tissues of the intestinal walls); this causes pain, nausea, and distaste for food, and this quickly brings about a fall in urea and acidity, and the rising alkalinity of the blood dissolves part of the 3 or 4 grs. on store, and floods the blood with uric acid; hence along with lead colic we have headache, depression, slow high tension pulse, and perhaps even epilepsy—all due, as I shall show, to the excess of uric acid in circulation; and anyone who will take the trouble to experiment with lead as I have done, can produce not only the fluctuations in uric acid (first, a retention, and then a plus excretion), but also all the signs and symptoms of its presence or absence from the blood just in the sequence I have mentioned them, and I have no doubt that any clinical observer will bear me out if I say that these are the main symptoms of acute and chronic plumbism, which can thus not only be explained but can be imitated at pleasure, either with lead itself or other members of the group, such as opium, cocaine, mercury, or acids.

Indeed, to such an extent is this the case, that I have come to believe that many cases of intestinal colic are due to urate irritation, of which urate of lead affords but a single instance, and in corroboration of this I may mention that salicylate of soda is a valuable remedy in all these forms of colic—a discovery which I made quite accidentally in my own case (see chap. x.)

It may be interesting to point out here that the similar rebound after iron accounts for the well known relapse of chlorosis or anæmia which have been treated by it. Here the iron is taken for a long time and in clearing the blood of uric acid stimulates nutrition and metabolism to an upward movement which continues for some time (weeks or months) after the metal has been left off; but as iron

[1] See "Lead Poisoning," by Professor T. Oliver, p. 102, *et seq.*; Young J. Pentland, 1891.

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relieves chlorosis by clearing the blood of uric acid, and clears the blood of uric acid not by eliminating it but by retaining it in the tissues, a time is certain to come when the iron is gone and the stimulation of nutrition has yielded to time, or some definite cause of depression (such as overwork), and then the chlorosis is certain to relapse and be worse than before; but as we shall see further on, when chlorosis is treated by a diet which clears the body and blood of uric acid and keeps them clear, the improvement of the blood is steady and continuous and there is no relapse.

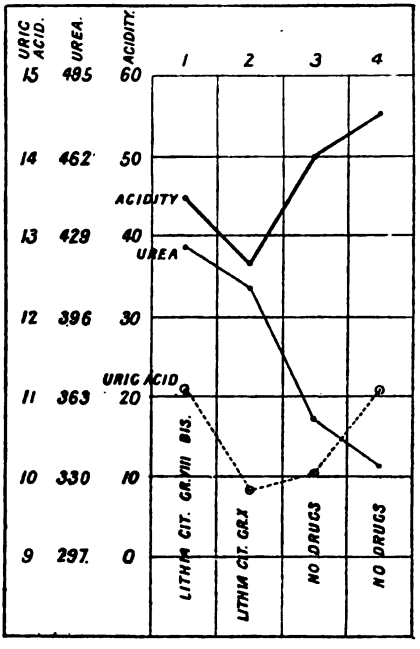

FIG. 14.—RETENTION OF URIC ACID PRODUCED BY LITHIA.

About lithia also I must say a few words, because it is an apparent exception—an exception, however, which beautifully proves the rule I have stated.

Fig. 14 shows the effect of taking citrate of lithia, and I am glad to see that the results I have obtained have been corroborated by the researches of Professor Oliver (see prev. ref. p. 107). On day 1 uric acid is nearly two grains below its ordinary relation to urea, and on day 2 it falls still further; on day 3 the lithia having

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been left off it rises a little, and on day 4 still more decidedly, getting above urea. And yet on day 2 we should have expected uric acid to rise as there was a fall of acidity, and again uric acid rose on days 3 and 4 in spite of a rise of acidity.

A fall of acidity similar to that on day 2 is, I believe, a constant result of taking lithia, but in this case the fall is never accompanied by a rise in the excretion of uric acid.

Now I believe that the ordinary effect of a fall in the acidity of the urine and a rise in the alkalinity of the blood, is that the phosphates of the blood have their power of dissolving uric acid increased, and that when there is a rise in the acidity of the urine and a fall in the alkalinity of the blood they have their power diminished; there is here obviously then some cause at work which prevents the phosphates in the blood from exercising their power of dissolving uric acid.

Sir A. Garrod has shown that urate of lithia is one of the most soluble of all urates, and yet I find that lithia diminishes the excretion of uric acid.

I may frankly confess that if I had been unable to find an explanation of this fact, I should long ago have given up my quest, and regarded uric acid as an insoluble enigma or will-o'-the-wisp, but fortunately the difficulty had already been solved for me by others, for in a reference (which I owe to Dr. Neale's Digest) to the *Lancet*, 1860, vol. ii., p. 185, I found that it had been pointed out in a work on chemistry by Rose ("Chemical Analysis," p. 15), that lithia given by the mouth was no use as a solvent of uric acid, because it "forms a nearly insoluble triple phosphate with phosphate of soda, or with the triple phosphate of ammonia and soda, salts generally present in animal fluids."

Here, then, was a simple explanation; the lithia I took by the mouth did not cause a plus excretion of uric acid because it never got to the uric acid, being waylaid by the phosphates and triple phosphates above mentioned; this would explain its not causing a plus excretion of uric acid, but why does it cause a minus excretion or retention? The answer is again simple, and it was in the first instance suggested to me by Mr. J. E. Saul, F.I.C. I have mentioned before that phosphate of soda is a good solvent of uric acid, and in presence of an alkali increases its excretion; now phosphate of soda is a normal constituent of the blood, and is generally there in presence of an alkali, *i.e.*, in a condition to act as a solvent of uric acid, so that the lithia in forming, as we are told, an insoluble compound (well known to chemists) with the above

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phosphates, removes from the blood one of the natural solvents of uric acid, and we now see not only why lithia causes no plus excretion of uric acid, but why it causes retention, and there is here no exception whatever to my law of solubilities.

In the test tube lithia is said to be a beautiful solvent of uric acid, but in the body its chemical combinations with phosphates not only prevent its action on uric acid, but put out of use a certain amount of phosphate also.

A year or two ago, at the suggestion of Sir Dyce Duckworth (see "A Treatise on Gout," p. 373), I investigated the action of manganese on the excretion of urates, and I found that it produced retention and some pains in the joints; so that it acts like calcium, iron, lead, mercury, and other metals, which form insoluble compounds with uric acid, and probably for the same reason.

Urate of calcium is very insoluble,[1] and chloride of calcium has an acid reaction, hence it probably diminishes the excretion of uric acid in two ways. I was led to observe that it did this by noticing that when administered internally it generally produced, to a very marked extent, a condition of happiness, well being, and good temper, which, as we shall see presently, is a sign of absence of uric acid from the blood.

I note also that Dr. G. Thin (*British Medical Journal*, vol. ii., 1891, p. 91) holds the opinion that the consumption of water containing lime brings about the development of gouty conditions; no doubt it acts in the same way as the contamination of water by lead; but if people would be at the trouble to reduce their animal food, and so their formation and introduction of uric acid, neither lime, lead, acids, or anything else would be able to injure them.

Acid phosphate of soda, or ordinary phosphate of soda given with a little phosphoric acid or in conditions of high acidity, brings about retention rather than plus excretion of uric acid.

In a similar way the salts of the mineral acids, sulphates, chlorides, &c., raise the acidity of the urine and produce a minus excretion or retention of uric acid; possibly they, to some extent, produce this result by changing the phosphates of the blood into acid phosphates, in which condition they are no longer able to act as solvents of uric acid, and I was able to show that while neutral phosphate of soda is a good solvent and produces a plus excretion of

[1] One in 2,800 parts of water; Sir A. Garrod's Lectures, *British Medical Journal*, January, 1883, p. 495.

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uric acid, it is unable to do this if a small quantity of sulphate of soda is given along with it (*Medico-Chirurgical Transactions*, vol. lxxii., p. 402).

Of opium I have elsewhere (*British Medical Journal*, November, 1889) written at considerable length, showing that it raises the acidity of the urine, probably by increasing the absorption of acids from the intestines, and when it does this it diminishes the excretion of uric acid and stores it in the liver, spleen, and joints, in the latter

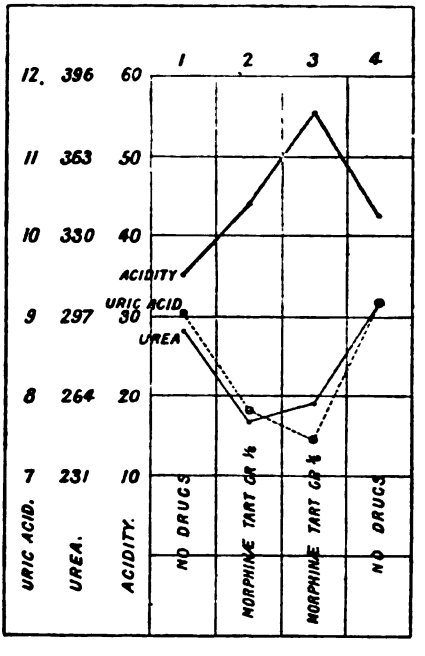

FIG. 15.—RETENTION OF URIC ACID PRODUCED BY MORPHINE.

of which it may cause pricking and shooting pains; it also produces the symptoms of absence of uric acid from the blood, namely, mental brilliancy, happiness, well-being, and good temper, for which it is so often resorted to. Fig. 15 shows the effect of taking two small doses gr. $\frac{1}{8}$ of tartarate of morphine, the first at 11 p.m. on day 2, and the second at 8 a.m. on day 3. The dose on day 2 came too late to produce much effect, as the large excretion of uric acid for the day was over long before 11 p.m.; it did, however, produce some rise of acidity. The dose on day 3, however, was taken pretty early in the

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morning, and it caused an increased rise of acidity, though urea rose but little, and uric acid on this day falls distinctly below urea. Probably, however, the chief rise of acidity caused by this second dose did not come till some 4 or 5 hours after it was swallowed, and by this time the alkaline tide was nearly over (see figs. 2 and 3), so that the effect on the excretion of uric acid was not very great. The dose, however, was very small, and as only one dose was taken, there was time for both the retention and the rebound in the same twenty-four hours, so that the effect would have shown better in hour to hour curves. There can be no doubt, however, that opium and morphine raise the acidity of the urine and diminish the excretion of uric acid, and that many of their physiological effects are due to their clearing the blood of this substance.

As with other members of this group (see previous remarks on lead), the first action of opium is followed by a rebound, in which the blood is flooded with uric acid, and the signs of its excess are seen in the headache, depression, and general misery, with slow high tension pulse which accompany this second stage of opium action (see fig. 34). These symptoms of mental misery and depression are those which drive the victim of the morphine habit to repeat his dose, to obtain once more the first-stage action of opium and temporary relief from his mental misery. I have pointed out that, in accordance with this reasoning, if salicylate of soda is given along with or in sequence to the first dose of opium, it prevents the opium causing any retention of uric acid, and then the opium rebound on the following day fails to appear or is very greatly modified.

This has led me to suggest (*British Medical Journal*, previous reference) the use of salicylates to aid the throwing off the morphine habit, and I know of at least one case where my suggestion has been followed with advantage.

A medical man, who had been in the habit of taking morphine for some time since a severe and dangerous illness in which it was used, wrote to me after the appearance of my article in the journal as to the best way of leaving it off, and I suggested, among other things, a plan of using the salicylates.

I have since heard from him that the plan was quite successful, that he was surprised how easily he was able to leave it off, and that he had no insomnia, and he ends by saying, "I shall always remember you with gratitude as having shown me the way to give up the habit, and I am sure that without the salicylates I should only have been able to do so with the greatest difficulty." How far other cases will bear this out remains to be seen.

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In my own person a dose or two of salicylates after a dose of opium completely prevents what I call the opium rebound, and there is no high blood pressure, headache, depression, or other ill-effect from the drug next day, but I have not myself tried it except after small doses of opium and morphine, not continued for more than a day or two.

I have also recently heard from my friend, Mr. Hope-Lewis, of Auckland, New Zealand, that in the case of one of his patients who took morphine, and suffered in consequence from intense irritation of skin and formication, 20 gr. doses of salicylate every four hours

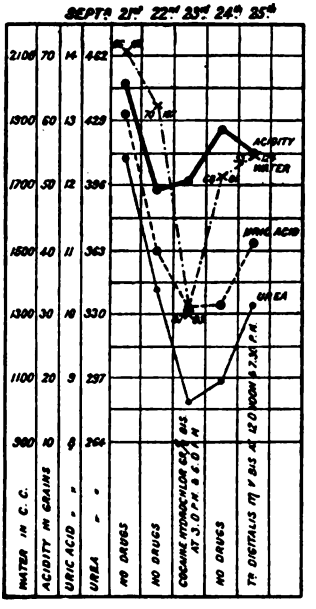

FIG. 16.—RETENTION OF URIC ACID PRODUCED BY COCAINE.

promptly removed these troubles, and this treatment would probably be worth trying in cases where the medicinal use of morphine causes irritation of the skin.

The action of cocaine, so far as uric acid is concerned, exactly resembles that of morphine, and like morphine it produces a first stage of happiness and well-being, followed later by a second stage of misery and depression, and cocaine has been indulged in to excess in the same way and for the same reasons that morphine has.

Fig. 16 shows the effect of two doses of gr. $\frac{1}{6}$ of hydrochlorate of cocaine taken at 3 and at 6 p.m. on September 23.

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On September 22 there was a great and decided fall of urea and acidity, and the fall of urea was continued on the 23rd.

As the result of this fall of acidity there was in the alkaline tide of the 23rd, as is shown by the scanty urine, only 37 cc. per hour, a decided plus excretion of uric acid, and some excess of it in the blood; and as this uricacidæmia was causing some uncomfortable symptoms, I took the cocaine with the view of getting some relief.

Here again, just as with morphine in the last figure, the effect would have shown better in hour to hour curves. The cocaine came too late to effect the large excretion of uric acid which had already taken place, hence uric acid exceeds its normal relation to urea by nearly one and a-half grains; but I have no doubt that but for the cocaine it would have been considerably higher.

The effect on acidity, however, was very marked, for on the 23rd, in spite of the further large fall of urea, it rose slightly; on the 24th it rose decidedly, and on the 25th it fell, in spite of a rise of urea, showing that something which had caused its rise on the 23rd and 24th had now been removed. On the evening of the 23rd, the cocaine produced very marked well-being with free capillaries and complete absence of mental depression and fatigue (see the similar effects of mercury in fig. 41), and though the urine of the night hours was not so high as that of the previous night it was two and a-half times as much as that of the day hours, which shows both that there were obstructed capillaries during the day, and free capillaries during the night (see remarks on excretion of water in fig. 3).

The effect of the cocaine was to prevent the continued fall of acidity on the 23rd, and to raise it decidedly on the 24th, and the effect of this on the uric acid was that it was not nearly so high on the 23rd and 24th, as with the great fall of urea on the 22nd and 23rd it would otherwise have been.

In my own case cocaine soon produces severe intestinal colic, so much so that I have been unable to continue or repeat my experiments with it as often as I should otherwise have done, but there is no doubt that it affects uric acid in the same way that morphine does, and produces identical feelings of happiness and well-being—indeed, each member of the group of drugs which diminishes the excretion of uric acid produces these feelings to a more or less marked extent.

The effects on acidity in this figure are quite clear, and there can hardly be much doubt that the physiological effects of cocaine are due to this, and its effects on the solubility of uric acid. Cocaine

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appears to cause slight constipation, and I think that it probably raises the acidity in the same way that morphine does, by causing coprostasis.

The first action of cocaine, like that of morphine, is to produce a low tension and quick pulse, due to free capillaries, and the result of this is, on the one hand, improved and quickened circulation in the brain, with mental brilliancy and well-being, and on the other relaxation of the vessels in the kidney causing a marked diuresis of a pale and watery urine.

Later on, just as with opium and other drugs I have spoken of, there comes a rebound. The uric acid held back and cleared out of the blood by the first action of the drug is again got into solution, the capillaries are greatly obstructed, and the tension high, hence the urine is scanty and of high specific gravity, and the mental condition one of lethargy and depression, with sleepiness (as in all high tension), and these miseries drive the sufferer to repeat the dose to get its first-stage action once more, and so lead the way to chronic cocainism.

I have very little doubt that cocaine, like morphine, owes a large part of its effects to its action on uric acid, and that salicylate of soda may be useful in cocainism just as in morphinism. For some interesting facts about the action of cocaine, see Dr. A. Fullerton, *Lancet*, February, 1891, p. 663.

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CHAPTER III.

Formation and Excretion of Uric Acid (*continued*).

Mercury is another very interesting member of the group of drugs which causes retention of urates. I have already written about it elsewhere (see *British Medical Journal*, vol. i., 1890, p. 1241).

Fig. 17 shows very well its action on uric acid, which on day 1 is a little below urea; on day 2 as the effect of half a grain of calomel it is far below urea, and on day 3, when no drugs are given, it bears about the same relation to urea as it did on day 1. Note also the very marked diuresis on day 2, corresponding with the greatest retention of urate, its clearance out of the blood, and consequent free circulation through arterioles and capillaries (see chapter v.).

Mercury sometimes causes, in my own case, considerable intestinal pain and colic, like that produced by cocaine, lead, &c.

I have also suggested that the low arterial tension and the diuresis, which are well known to be brought about by the action of mercury, are due to its effects on uric acid, for other drugs having similar effects on uric acid produce similar symptoms as we already know.

With regard to the action of mercury, Sir A. Garrod does not, so far as I know, say anything as to the solubility of urate of mercury, and it is not mentioned in his table of solubilities of urates (*British Medical Journal*, vol. i., 1883, p. 495).

It seems to me, however, that it is very probable that mercury causes retention of uric acid, and clears it out of the blood for the same reason that iron and lead do so, namely, that their urates are insoluble, and Mr. J. E. Saul, F.I.C., has kindly given me the following statement as to the solubility of the urates of mercury:—

"I find that a solution of neutral lithium urate, treated with solution of mercuric chloride, yields a curdy white precipitate practically insoluble in cold water. On boiling, slight decomposition

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occurs, the precipitate becoming yellowish—possibly owing to the formation of an oxysalt. On treating the first-mentioned precipitate with acetic acid, or a trace of hydrochloric acid, solution, slowly in the former case and immediately in the latter, takes place. Borax or alkalies exercise no solvent action. These experiments show that neutral mercuric urate is insoluble, but that the salt will dissolve in the presence of acid, though doubtless with decomposition.

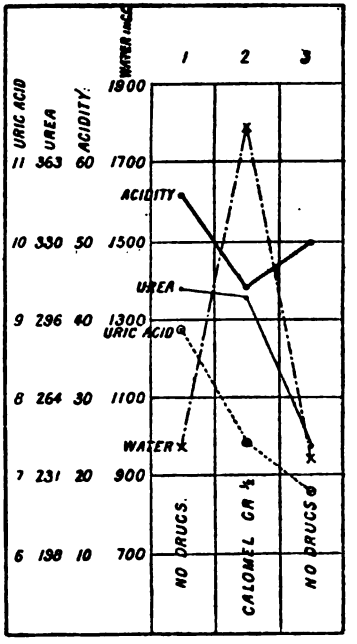

FIG. 17.—RETENTION OF URIC ACID PRODUCED BY MERCURY.

Note that on day 2 uric acid falls in spite of a marked fall in acidity, which, apart from the action of mercury, would have made it rise.

"I have also examined the behaviour of a neutral alkali urate with solution of mercurous nitrate. I find that a yellowish precipitate, insoluble in water, is immediately produced; the precipitate rapidly darkening in colour, and ultimately becoming grey-black from reduction. In the presence of nitric acid no precipitate is obtained, but if acetic acid be substituted, a partial precipitation slowly takes place.

(*Signed*) "J. E. SAUL."

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From this we see that there is good reason to believe that the urates of mercury are insoluble in water, in neutral solutions, in alkalies, or in solution of borax, and as the blood may be practically regarded as an alkaline solution, they are probably insoluble in the blood.

Therefore, mercury diminishes the excretion of uric acid in the urine, clears it out of the blood, and retains it in the body, because it forms with it an insoluble compound, and it is therefore a single instance of my law of solubilities. And the well-known action of

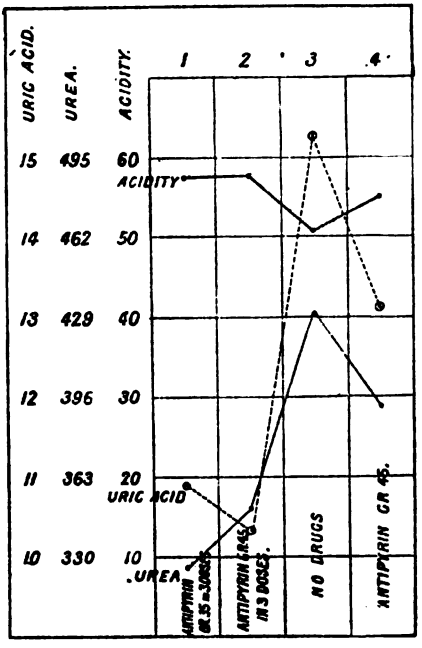

FIG. 18.—RETENTION OF URIC ACID PRODUCED BY ANTIPYRIN.

mercury on the pulse-rate and tension, and the flow of urine, are also single instances of the laws I have formulated with regard to the relation of these to uric acid. Some have objected to this that the amount of uric acid held back by the mercury is much more than could possibly be combined with it as an urate ; but, as I shall have to point out in chapter iv., the mercury, if it clears the blood of uric acid for quite a short time as one or two hours, starts an upward metabolism with a rise of urea and urinary acidity, and a

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fall in the alkalinity of the blood, and this latter causes a further retention of uric acid, which may continue for six or eight hours more. This effect of mercury is better seen in hour to hour curves rather than in day curves, as in fig. 17, but it is seen to some extent in fig. 41.

I think it is extremely probable that the urates of other metals, such as zinc and silver, are also insoluble, and indeed Haycraft's process for the estimation of uric acid depends upon the insolubility of the urate of silver, and that the so-called tonic action of these drugs, as of iron and manganese, and indeed of acids, is really due to their clearing the blood of uric acid, and so improving the circulation in the brain and other portions of the nervous system. It is interesting to remember that zinc, like mercury and lead, may produce colic (Ringer, "Handbook of Therapeutics," ed. xii., p. 254).

I have suggested that antipyrin cures headache by acting as an acid, and its administration is always followed by a rise in the acidity of the urine.

Fig. 18 shows the effects of antipyrin on the acidity, which on days 1 and 2 rises and remains high, and with this on day 2 uric acid falls below urea (probably the antipyrin came too late to affect the alkaline tide of day 1, so that the greater part of the urate excretion had already taken place). On day 3 no drug is taken, and acidity falls decidedly, in spite of the fact that urea has risen, and in normal conditions acidity would have risen also; but the antipyrin had raised it so much on the previous days that the moment it was withdrawn down it fell. On day 4 antipyrin was again given, acidity rose in spite of falling urea, and uric acid was brought down much nearer urea.

We can now see how antipyrin cures a uric acid headache, by raising acidity and clearing the blood of uric acid, all the signs of which mental well-being, low tension, quick pulse (fig. 34), joint pains and diuresis it also produces; it therefore acts just as an acid, and I for one should prefer to give an acid in its place.

Strychnine causes a marked rise in urinary acidity and cures headache. I have suggested that the rise of acidity is due to its improving the condition of the stomach and promoting digestion and absorption of food, which in headache with nausea is often at a standstill; like other things that raise acidity, it often causes pricking and shooting pains in the joints.

The administration of hyposulphite of soda produces a very marked rise in acidity of the urine, possibly by the formation of sulphurous acid or the further oxidation of sulphur, and it pro-

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duces all the symptoms and effects of the administration of a strong dose of acid (see fig. 11).

And it has appeared to me to be very probable that nitrites may act in much the same way, and by the formation of nitrous acid may diminish the alkalinity of the blood and raise the acidity of the urine, which it is easy to demonstrate that they do (see figs. 19 and 20).

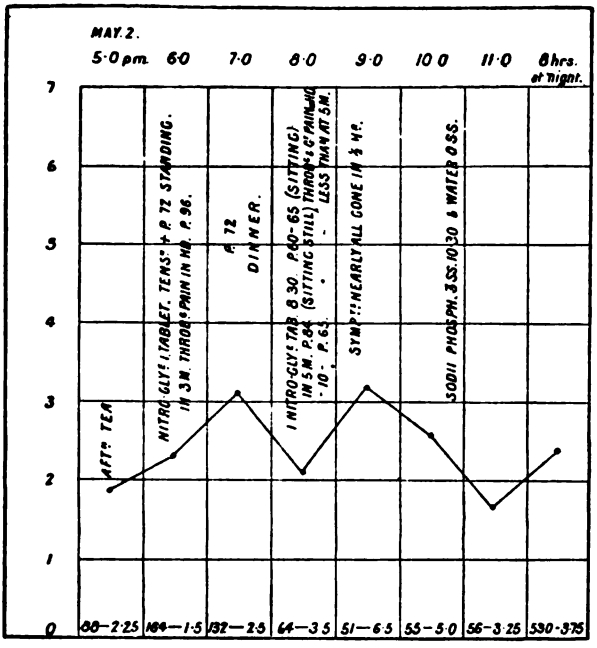

FIG. 19.—EFFECTS OF NITRO-GLYCERINE ON THE ACIDITY OF THE URINE.

This being granted, it appears to me that the well-known effects of nitrites on the pulse rate and tension may be explained by their action on uric acid as an acid.

And in favour of this supposition is the fact that an acid injected into a vein produces, I believe, just the same effect on the pulse as a nitrite does. So far as my observations go, nitroglycerine taken by the mouth does not exert its maximum effect on pulse tension for some seven or eight minutes, and in the case of a volatile substance rapidly diffused throughout the body this is

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a considerable time; and as regards uric acid, I take it that the action of an acid or anything that interferes with its solubility in the blood is as rapid as that of precipitation in a test tube, and is practically instantaneous. I do not suppose that the uric acid is precipitated in crystals, but it is rapidly rendered less soluble in the fluids, and is held back in certain organs and tissues in accordance

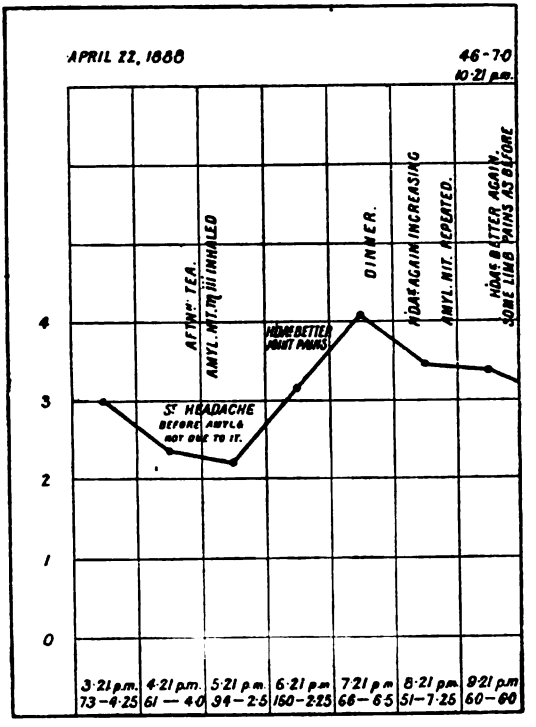

FIG. 20.—EFFECT OF NITRITE OF AMYL ON THE ACIDITY OF THE URINE.

with the theories of Sir A. Garrod, and I shall presently have to bring forward evidence that anything which clears the blood of uric acid either allows the arterioles all over the body to relax or frees the capillaries, and thus rapidly reduces blood-pressure, the rapidity of the fall of pressure depending on the rapidity and completeness with which the uric acid is driven out.

In the *Lancet* (vol. i., 1891, p. 1323), it is pointed out that the administration of sulphurous acid, and even its inhalation, will

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reduce the alkalinity of the blood, which is greatly in favour of my argument as to the action of nitrites, and my results as regards the acidity of the urine when hyposulphites or sulphur in other forms are taken. The same article shows that sulphurous acid is largely used in the preservation of wine and vegetables—a fact of considerable importance for gouty subjects.

It is certainly remarkable what very small quantities of these acids (nitrous, sulphurous, &c.) will produce marked effects on the excretion of uric acid, and in this they do not stand alone, for quite small quantities of salts of the mineral acids will produce similar effects, as I have had experience in very numerous instances. And thinking over this matter, it has occurred to me that the solvent power of phosphate of soda for uric acid and urates may help us to explain this apparent difficulty, just as they helped us to explain the difficulty in the case of lithia. If a little lithia produces marked retention of uric acid by throwing out of action a quantity of its natural solvent, phosphate of soda, a minute quantity of acid may possibly have the same effect on the phosphate, and may change a large quantity of it from $Na_2H.PO_4$ to NaH_2PO_4; then the effect on the solubility of the urate will be proportional to the amount of phosphate which is thus thrown out of action, and not to the relatively minute amount of acid which caused the change.

Hence the stimulant action of all kinds of acids is dependent upon the conditions present in the blood and fluids of the body; if these are favourable to diminished alkalinity they may produce a large effect, if unfavourable, little or none: and so the action of a given dose will vary considerably not only in different individuals, but in the same individual at different times.

With regard to the action of the nitrites, the researches of Professor Leech (Croonian Lectures, 1893) seem to show that those substances undoubtedly exercise a direct depressant action on muscular tissue. They also show, however, that these compounds are decomposed in the stomach, giving off nitrous acid, which is absorbed into the blood and importantly affects its composition and reaction; thus Professor Leech says (*Lancet*, vol. i., 1893, p. 1502), "When absorbed it (nitrous acid) is no doubt at once converted into an alkaline nitrite, for it can replace carbonic acid in its sodium compounds and convert normal sodium phosphate into acid phosphate, sodium nitrite being at the same time formed."

Now, the result of this conversion of normal phosphates into acid phosphates, is a rise in the acidity of the urine, which I have just pointed out that the nitrites produce; and as the normal

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phosphate of sodium is a good solvent of uric acid while the acid phosphate is not a solvent at all (see *Medico-Chirurgical Transactions*, vol. lxxii., p. 399), the blood becomes, as a result of this action of the nitrites, a bad solvent of uric acid, and ceases to hold it in solution, and as a result of this the capillaries will be freed and arterial tension reduced.

It seems probable, then, that the action of the nitrites on arterial tension is the resultant of two forces; first of all, of the muscular depressant action weakening the muscle fibre in the heart and the vessel walls generally, an action similar to that of tobacco, lobelia, and other depresso-motors (see *Brain*, Spring and Summer Number, 1893, p. 245); and second, of the general freeing of capillaries which all substances produce which clear the blood of uric acid.

In this connection I was much interested to hear from my friend Surgeon-Captain Newland that a friend of his, Dr. Saunders, had been using nitrites in ague to shorten the cold stage and bring on the sweating stage, apparently with good results.

Sir A. Garrod tells us,[1] how he found uric acid in normal blood, and an excess of it in that same fluid, and in the serum of a blister in gout, and the same in lead poisoning;[2] and he there also shows that lead given medicinally diminishes the excretion of uric acid in the urine; and he remarks[3]—"It would appear, therefore, that in individuals impregnated with lead the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion."

This is in absolute and complete accord with my results,[4] and I should apply the same reasoning not to lead only, but to all substances that diminish the excretion of uric acid in the urine; and for my part I have not met with any evidence that there is, or ever has been, an excess of uric acid in the blood due to increased formation, *i.e.*, above the relation to urea of 1 to 35. I believe that for every 35 or 40 grs. of urea that are formed in the body, 1 gr. of uric acid is also regularly and punctually formed, but no more. The 40 grs. of soluble urea are excreted with practically absolute certainty; but the insoluble uric acid, though in much smaller quantity, is very apt indeed, from various causes, to lag behind and be retained in the body.

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[1] "Gout and Rheumatic Gout," 3rd edit., p. 84, *et seq.*

[2] Ibid., p. 240.

[3] Ibid., p. 243.

[4] See *Med. Chir. Trans.*, vol. lxxi., p. 284.

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We shall see also later on, with reference to the above quotation from Sir A. Garrod, that the uric acid is probably not in excess in the blood at the time when under the influence of lead it is diminished in the urine, but it subsequently appears in excess in the blood when that which had been held back by the lead is got into solution by alkalies or other solvents in the blood, but as soon as it is in excess in the blood it begins also to pass in excess in the urine.

My investigations, I believe, prove absolutely that an excess of uric acid in the urine above the relation to urea of 1 to 35 comes from an excess in the blood, and that when the uric acid in the urine is diminished below that relation (say 1 to 45) there is little or none in the blood, because every particle that gets into it from the kidney by the renal vein is at once caught up, so to speak, and stored in the liver, spleen, and other tissues.

According to Sir A. Garrod's theory, the antecedent elements of uric acid come probably from the liver to the kidney, and are there formed into urate of ammonium.

By far the largest part of the urate thus formed (say for the sake of a definite quantity nine-tenths) passes at once down the ureter and leaves the body; but the remaining one-tenth may, under certain conditions, pass, according to Sir A. Garrod, into the general circulation through the renal vein; and when there it is attracted differently by different organs, being liable to retention in certain organs which are less alkaline than the blood, and therefore less able to hold it in solution.

It is this residue of uric acid plus that which is directly introduced preformed in food which, according to my interpretation of my results by the light of Sir A. Garrod's hypothesis, furnishes all the uric acid of pathology. If the whole of the urate formed in the body had passed down the ureter as soon as formed, there would have been much less trouble, and to bring about the complete excretion of all that is formed, as well as to keep down the quantity introduced, must be the aim of all treatment.

It seems extremely probable that the alkalinity of the kidney structure determines to some extent how much of the urate formed in it shall be at once excreted, and how much shall be temporarily kept back with a chance of eventual passage into the general circulation.

Possibly the pathological urate deposits found in the kidney after death are mere exaggerations of the normal retention which constantly occurs to some extent during life.

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When urea is high and especially when it is above the physiological relation to body weight, it seems probable that the alkalinity of such organs as the liver, spleen, and kidneys will be diminished just as the acidity of the urine is increased; so that when urea is too high we shall get increased retention of uric acid in these organs (see fig. 65).

To render my meaning clearer, I shall now speak of definite quantities. If a man forms, as my results render it probable that he does, 1 gr. of uric acid for 35 grs. of urea, let us suppose that he forms in twenty-four hours 12 grs. of uric acid and 420 grs. of urea.

The whole of the urea and 10 grs. of uric acid are excreted, giving a relation in the urine of 1 of uric acid to 42 of urea; and 2·0 grs. of uric acid are held back in the kidney, passing gradually into the general circulation.

Once in the general circulation the urate is rendered insoluble and kept back in certain tissues (according to Sir A. Garrod, the liver, the spleen, the joints and the fibrous tissues), because of their relatively diminished alkalinity and consequent deficient power of holding urates in solution.

Next day let us suppose that again 420 grs. of urea are formed and excreted, but this time uric acid is in excess of its normal relation to urea, say 1 to 30, *i.e.*, 14·0 grs. are excreted.

But according to our hypothesis only 12 grs. were formed, and therefore 2·0 grs. must have come from somewhere else, even supposing that all the uric acid formed in the kidney on this day passed direct down the ureter. It is now, of course, evident that the amount of uric acid held back and retained on the previous day furnishes just what is required for the excess in excretion of this day, and thus the excretion of uric acid, but not its formation, fluctuates from day to day.

We can now explain completely why the excretion of uric acid is large during the "alkaline tide" of the morning, and small during the acid tide of the night hours. It is a simple question of solubility in the blood (see remarks on fig. 3).

Further, by giving alkalies the excretion can (as I have long pointed out)[1] be at any time increased, or by giving acids diminished.

But if the stores in the liver, spleen, and joints have been swept

[1] See *Journal of Physiology*, vol. viii., p. 216; and *Brit. Med. Jour.*, 1890, vol. xii., p. 124.

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out by the repeated exhibition of solvents, then there is no drug which will cause a plus excretion of uric acid till there has been again some retention and accumulation in these structures (see figs. 7 and 8).

These facts account completely for all the conditions in which an excess of uric acid is met with in the body, and failure of excretion will soon keep back as much as is ever found in the body before or after death.

On the other hand, the theories of excessive formation (*i.e.*, formation of uric acid in excess of the normal relation to urea, about 1—35 or 1—40), or of deficient oxidation are at once incompatible with the facts I have brought forward, and unnecessary for the explanation of the phenomena of disease; and as we shall see further on the whole of the diseases treated of in this book may be prevented or cured without the least reference to them, and we should be much nearer the truth if we attributed them to poisoning by meat and tea, which can be both demonstrated and prevented, rather than to the above-mentioned theories, which are wholly devoid of foundation in fact.

Sir A. Garrod has also pointed out[1] that there is little or no uric acid in the blood in acute rheumatism, and he proceeds to draw the conclusion that this disease is not due to uric acid. I have given elsewhere[2] my reasons for thinking that this conclusion may require some revision, and I shall have something to say about it further on. My facts are in complete accord with those of Sir A. Garrod; it is only regarding the conclusion to be drawn from them that I venture to differ from him.

One further fact about uric acid is, I believe, mentioned in all text-books of physiology, viz., that it is found as a practically constant constituent of the spleen pulp after death.

It is interesting to note that (as I have several cases to show) uric acid is nearly always present in great excess in the urine in cases of enlarged spleen, as in splenic leucocythæmia, and it has been shown by others to be in excess in the blood in this condition.[3]

In several cases of this kind I examined the urine for eight or ten consecutive days, the whole excretion being saved; and in these, over the whole period, the average relation of uric acid to urea in

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[1] Reynold's "System of Medicine," 1st edit., vol. i., p. 897.

[2] *Med. Chir. Trans.*, vol. lxxiii., "Salicin compared with Salicylate of Soda," &c.

[3] See Salkowski und Leube, *Die Lehre vom Harn*, *p.* 88.

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the urine was 1—12 or 1—14. It is little wonder then that under these conditions an excess of uric acid should have been found in the blood, the excess in the urine being, as I have said, the index of this.

It may be remembered also that I have shown that there is generally an excess of uric acid in the urine excreted during an epileptic fit (see cases in chapter vii.). Sir A. Garrod found excess of uric acid in blood drawn during an epileptic fit, and has pointed out the alternation between gout and epilepsy—a fact which my results and conclusions completely explain. And if the liver, spleen, and joints are less alkaline, as Sir A. Garrod has pointed out, than other tissues, any uric acid coming to them in the blood stream is rendered, as Sir A. Garrod puts it, "less soluble and more easily retained," and we can at once explain why these tissues are frequently found after death to contain considerable quantities of uric acid.

In order to estimate the amount of uric acid in the blood and tissues I first of all made a water-extract of them by a process described by Salkowski and Leube,[1] and then having evaporated and cleared my solution, I applied Haycraft's process to it, just as in the case of urine (see chapter xviii., also my remarks as to my results with this process on p. 8).

In specimens of human blood obtained during life, I found quantities of uric acid ranging from ·03 per cent. in a case of cerebral hæmorrhage to ·0006 per cent. in a case of cellulitis, the blood flowing from incisions made into the inflamed tissue. In the blood of a fatal hæmoptysis in a case of fibroid phthisis, the patient being at the time on salicylate of soda, I found ·0065 per cent. of uric acid, and having plenty of blood to work on in this case, I was able to estimate the quantity more accurately than is generally possible with small samples.

With regard to the very small quantity of urate in the blood from incisions in an arm affected with cellulitis, Sir A. Garrod, it may be remembered, has pointed out ("Gout and Rheumatic Gout," pp. 187 and 274), that there is no urate in the fluid of a blister or in blood drawn directly over the inflamed joint in gout, and suggests as an explanation that inflammation destroys uric acid.

My facts are in complete accord with his; but I think the explanation is that local inflammation means local reduction of alkalinity, so that all urate coming to that part is rendered in-

[1] *Die Lehre vom Harn*, p. 94.

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soluble and retained, and the blood or serum which have passed through the inflamed part are practically cleared of uric acid. So in acute rheumatism the urate is in the joints and the blood is cleared of it; but in gout (a more local disease) only that part of the blood which has passed through the inflamed area is cleared of urate.

Here also we have a complete explanation of the well-attested facts as to the alternation of gout with headache, epilepsy and mental depression, for uric acid, as we know, attracts uric acid, and where accumulations are going on in certain joints or fibrous tissues these tend to take up all the urate that comes past them in the blood, and hence perhaps for weeks, months, or even years, the blood is kept relatively clear of uric acid, and headache, epilepsy, and depression are remarkable by their absence.

In specimens of human blood obtained after death from the heart cavities, it seemed to me that when the joints contained urates there was more in the blood than when they contained none—thus eleven cases with urate deposits gave ·03184 per cent. of uric acid in the blood, and eleven cases in which there were no urates gave an average of ·02255 per cent.

Then I noticed that in the blood of cases dying of pneumonia there was generally a great excess of uric acid, and five cases of this kind gave an average of ·03742 per cent.; but in a case of pneumonia and delirium tremens the blood obtained by venesection, while the temperature was 102°, only contained ·0006 per cent., and this fact enables us at once to explain the great excess met with in the blood of these cases after death.

During the acute onset and high fever of the first two or three days of a pneumonia, there is a great rise of acidity, or what amounts to the same thing, a fall in the alkalinity of the blood and tissue fluids, and this drives all the uric acid out of the blood, and retains it in considerable quantity, for the reasons previously given, in the kidney, liver, spleen, and possibly the joints and other tissues. There it goes, and there it remains so long as the fever is able to keep down the alkalinity of the blood and tissue fluids; but when the temperature falls, the alkalinity of these fluids quickly rises, and the retained uric acid is soon got again into solution, thus coming to be in excess in the blood, and passing from it in excess in the urine; the excess of uric acid in the blood accounting for the headache and mental depression and suicide, with slow high tension pulse and subnormal temperature, which are so common in convalescence from acute febrile diseases.

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If, however, the patient dies, precisely the same thing occurs. For some hours before death there is great failure of nutritive processes; and even if the temperature keeps up, the alkalinity of the blood and fluids may rise, owing to the failure of nutrition and of respiration. Hence uric acid is dissolved out from its places of deposit, and is in excess in the blood at the time of death, this excess being, as will now be understood, the direct result of its expulsion from the blood and retention in certain organs during the diminished alkalinity of the early stages of the acute fever.

Then again, cases in which at the time of death the temperature was high and rising, as in meningitis, yield generally only a small amount of uric acid in the blood; but there are several exceptions to this rule, due probably to the fact above mentioned, that in spite of high temperature the alkalinity of the blood and fluids may be rising, owing to general failure of nutrition; and in one case of pyæmia with embolic hemiplegia I got quite a large amount (·05426 per cent.) in the blood, in spite of a temperature rising to 104° at the time of death; and in another case of cerebral lesion about the same amount. With reference to cases of this kind, I would suggest that the cerebral changes (softening) in connection with the hemiplegia would cause the passage through the blood of a large amount of phosphates;[1] and that, as I have pointed out,[2] certain phosphates of soda, potash, and ammonia are powerful solvents of uric acid, and greatly increase its excretion, and no doubt its quantity in the blood for the time being.

Two cases, in which the blood contained ·01243 and ·05880 per cent., had ·06384 and ·08668 per cent. = 4·5 to 6·1 grs. per lb. in the spleen respectively, the relative excess in the spleen being in accord, as previously mentioned, with all that is already known on the subject.

Nine cases of morbus cordis gave an average of ·03350 per cent. in the blood after death.

For the rest my results show that the blood after death generally contains some little uric acid, though the amount is subject to considerable variation, the largest quantity met with being ·0744 per cent. in a case of pneumonia, and the smallest ·01008 per cent. in a case of meningitis.

Eight specimens of liver yielded an average of ·05928 per cent.,

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[1] *Zuelzer, Semiologie des Harns*, p. 89; and *Brain*, vol. ix., p. 364.

[2] *Med. Chir. Trans.*, vol. lxxii.

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= 4·2 grs. per lb., and the liver of a six months' fœtus that did not survive its birth yielded ·003 per cent., = ·2 grs. per lb.

Five specimens of spleen yielded an average of ·06412 per cent., = 4·5 grs. per lb., or slightly more than the liver.

Nine specimens of kidney yielded an average of ·0513 per cent., = 3·6 grs. per pound, that is, less than either the liver or spleen. One kidney (not included in the above), from a child of thirteen days old, which contained well-marked uric acid infarcts, yielded the very large quantity of ·23 per cent., = 16·4 grs. per pound, or more than four times as much as the above specimens. My best thanks are due to my colleague, Dr. S. W. Wheaton, who kindly placed this most interesting specimen at my disposal. He informs me that the uric acid of these infarcts, which were plainly visible in the medulla of the kidney, was seen under the microscope to be both in the tubules and in the connective tissue round them, which, according to authorities on the subject, is generally the case (see Zeigler, *Pathologische Anatomie*, vol. ii., p. 333). The kidney of the above-mentioned six months' fœtus contained ·002 per cent., = ·14 grs. to the pound.

A piece of human psoas muscle contained apparently ·028 per cent., = 2 grs. to the pound. It may also be interesting to mention here that half-a-pound of beef-steak yielded ·019 per cent., = 1·3 grs. to the pound, and that I found the equivalent of ·697 per cent. =49 grs. to the pound, in some meat juice, and of ·883 per cent. = 63 grs. to the pound in some meat extract (see also chapter xvii. and remarks on these quantities there).

In a case in which the blood from the heart had ·06904 per cent. (a very large quantity), the urine drawn from the bladder gave a relation of uric acid to urea of 1 to 9·4, a very great excess also. In a case with ·02384 per cent. in blood, the relation in the urine was 1 to 27, *i.e.*, much less in both. In another case there was ·03024 per cent. in blood, and relation in urine 1 to 29. And in another, ·03914 per cent. in blood, and urine relation 1 to 10, *i.e.*, a considerably greater excess in the urine than in the blood.

And in another case ·06888 per cent. in the blood, and a relation of uric acid to urea in the urine found in the bladder of 1 to 18, and the percentage of uric acid in the urine was ·03696. The liver in this case contained ·088 per cent., = 6·3 grs. per pound. The amount in the spleen was not estimated, but no doubt, as in other cases, it contained nearly as large an amount as the liver. I would remark, in passing, that these facts seem to me to be strongly in favour of my argument that the excess in the urine is an overflow

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from the excess in the blood, and that the excess in the blood again is due to its dissolving out and taking up some of the stores in the liver and spleen.

A similar explanation can be given of the greater quantity of uric acid in the blood of cases which have urates in their joints; here the blood has obviously an additional storehouse from which supplies of uric acid can be drawn. And in cases of chronic wasting disease, it is easy to demonstrate that it does draw on it; that for weeks together there is, as I have observed, an excessive excretion of uric acid in the urine, and after death erosion of joints is found, but all or nearly all the urate has been dissolved out of them.

These results show that when there is excess in the blood there is also excess in the urine, but we must not, I think, press the matter more closely than this, or we shall get into difficulty and error.

We must remember that the urine found in the bladder after death is the excretion possibly of several hours during which the amount of uric acid in the blood fluctuated considerably, so that nothing more than a general rough relation between the two can be expected. It is not a little remarkable that in upwards of sixty specimens of *post-mortem*, blood examined by me it should have been possible to throw into groups the diseases which caused death, in accordance with the amount of uric acid or xanthin found. Thus a specimen containing a very large quantity might come from a case of pneumonia or cerebral hæmorrhage, one with moderate quantity from a case of any wasting disease, especially if there are urates in the joints, while one with a very small quantity would probably come from a case of meningitis or other disease accompanied by acute fever right up to the time of death. I would also point out that in thus fluctuating with the presence or absence of fever in the hours preceding death this substance in the blood follows exactly the laws that govern the excretion of uric acid in the urine during life. It also corresponds quite definitely with the excretion of uric acid in the urine just before death, and this may be linked with what I shall have to point out further on, that the swallowing of any xanthin compound increases the excretion of uric acid in the urine.

I have also made a few examinations of the blood and organs of animals.

Dog killed after operation under chloroform: blood contained ·00168 per cent. That of another dog ·00336 per cent., and the urine of this dog obtained at the time of death gave a relation of uric acid to urea 1 to 85, which is a large amount of uric acid for a dog.

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The urine of a cat gave a uric acid urea relation of 1 to 110.

The blood of several other dogs contained very small traces, about ·00126 per cent.; their livers from ·04 to ·02 per cent., and their urine at the time of death gave uric acid urea relations of 1 to 136 to 1 to 144.

It may be difficult or impossible to say in a given case that the substance thus found in the blood is uric acid, as the quantities available may be too small to give a satisfactory murexide reaction; but we must not lose sight of the fact that uric acid has over and over again been found in the blood, and that it has been so found just in the very conditions with which we were dealing and under which it is always to be met with in excess in the urine.

I then tried to work on the urine of a single animal (dog) to collect it day after day, and to try and alter the uric acid urea relations by diet and drugs.

A bitch, weighing 11lbs., was kept in the ordinary form of cage for collecting the urine, and was fed on 6·6 oz. boiled horse, 5 oz. milk, and 5 oz. of water.

The urine was passed at very irregular intervals, but the uric acid urea relation was 1 to 87 on the first day, and 1 to 165 on the fifth and last day of the above meat diet; urea being 25 grs. per lb. So that it rather appeared that the meat diet in the dog, as in man, diminishes the excretion of uric acid at first.

The animal was then put on a diet of porridge O. i., and milk O. iss., which, however, it took very badly; on this urea fell very greatly down to 13, and eventually even to 5 and 6 grs. to the lb., and uric acid increased relatively, being 1 to 146, 1 to 110, and 1 to 98.

On the last day of this experiment I gave hyposulphite of soda in the milk with the object of diminishing the uric acid, and apparently with some success, as the relation altered to 1 to 143.

The animal, which now weighed 13 lbs. (an increase of 2 lbs.) was killed, and the blood, liver and kidneys examined.

The blood contained	·0003	per cent.
,, liver ,,	·0287	,,
,, kidneys ,,	·0460	,,

The very small quantity in the blood was in accordance with the diminution in the urine, which again was probably due to the drug given, and this further corroborates what I have said above as to the general correspondence between the quantities in the blood and urine.

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I would point out also in reference to the question of formation *v.* introduction, that this bitch probably formed absolutely no uric acid, for as she excreted 25 grs. of urea per pound, or 275 grs. a day, and uric acid in about the average relation to it of 1 to 120 or 2·2 grs., the whole of this uric acid might have come direct from the meat eaten, for if there is as much uric acid in horse as in beef (see chapter xvii.), 6·6 oz. of horseflesh would supply 2·4 grs. of uric acid, and it thus seems to me that the whole of the uric acid in the urine of these carnivora may be due to introduction, while their formation is nil.

In other dogs I attempted to increase the uric acid in the blood and urine by giving salicylate of soda, but this failed completely. There was practically no uric acid in the blood of either of the two animals thus treated, nor was there any increase of uric acid in the urine, the relation being in this latter fluid 1 to 140 to 1 to 150. Both urines gave a strong salicin reaction with perchloride of iron, so that the drug was plentifully absorbed and excreted.

Now, I think that this is a very interesting fact, that salicylate of soda, which has such a great power over the excretion of uric acid in man, should produce absolutely no effect on it in dogs.

I think, however, that I can see my way to some explanation of the fact, as in all that I have written about the action of salicylate of soda in man, I have always been careful to point out that acids aid, and alkalies hinder, its solvent action on urates (see p. 37, and fig. 62). Now, strange as it may seem, the acidity of dogs is very low indeed; and the bitch that I fed on horse-flesh, though excreting 25 grs. of urea per lb., only excreted acid to the equivalent of 1 grain of oxalic acid for 16 to 17, or even 18 grs. of urea, the acidity urea relation being 1 to 18; but in man, as I have shown in my own case, it is 1 to 6·3; so that this dog (a carnivore) excreted only one-third of the acid per grain of urea that we do; probably, therefore, its blood was far more alkaline than that of a man on the same diet, and hence the salicylate failed to affect the uric acid as it does in man (see also cases in chapter xvi).

With regard to the above relation of acidity to urea, Dr. A. Auerbach has pointed out (Virchow's *Archiv*, 98-3, p. 512) that no amount of acid that can be given will render the blood of carnivora acid, as they form ammonia to neutralise the acid, and no doubt something of the sort accounts for the very low acidity in the dog above mentioned.

I think, also, that the fact that man has not this power of forming ammonia to neutralise acids, or has it only to a very slight

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extent as compared with the carnivora, is a further proof that he is physiologically a frugivore and not a carnivore.

In two monkeys, the organs of which were very kindly placed at my disposal by my colleague, Dr. H. H. Tooth, I found in the blood about ·00441 per cent., = ·3 grs. per lb., in the liver ·060 per cent., = 4·2 grs. per lb., in the kidneys ·050 per cent., = 3·5 grs. per lb., and in the muscles of the back ·017 per cent., = 1·2 grs. per lb. of uric acid or xanthins. (Here, just as in man, the kidneys contain less than the liver.)

Alongside of my results it may be interesting to mention those of a well-known author, Professor R. v. Jaksch, of Prague, who in a paper "Ueber uricacidæmie" (*Deutsch. Med. Wochenschrift*, Aug., 1890, p. 741), gives the results of his investigations into the uric acid in the blood, together with an explanation of the causes that tend to increase its quantity.

His facts in the main are in accord with my own; but his conclusions from them are based on what I believe to be a completely erroneous theory, that all increase of uric acid in the blood is due to deficient oxidation, and not, as I have for some years been endeavouring to show, to a retention of it in the body, together with daily introduction, leading to subsequent increased excretion, the increase passing through the blood on its way to the kidneys.

Now, Professor v. Jaksch relates that he found no demonstrable uric acid in the blood of nine healthy individuals, and the same in cases of tabes, multiple sclerosis, polyneuritis, and cerebral tumour.

I should have expected that if there was any wasting in the diseases mentioned there would have been some uric acid in the blood, but as all the facts are not given, it is impossible to draw any definite conclusion.

To reason from the results in healthy subjects, it would be necessary to state the time of day at which the blood was drawn; for my researches make it extremely probable that there is some appreciable amount of uric acid in the blood of every one for an hour or two during the "alkaline tide" of the morning (fig. 3, also 45, and remarks on it), and that the excess in the urine commonly met with at this time is an overflow from some excess in the blood; and, as I have elsewhere pointed out, the mental condition and the rate and tension of the pulse, the temperature and other things, often point to excess of uric acid in the blood in the "alkaline tide."

Again, in nine cases of typhus, Professor v. Jaksch found no uric acid in the blood; but it was present in one case after the

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fever had gone. Similarly in intermittent fever there was no uric acid during the fever, but when the temperature fell uricacidæmia supervened.

This, it will be noticed, is in complete accord with my results and reasoning. .When there was fever the alkalinity of the blood was diminished, the uric acid became less soluble in it, and was retained in the liver, spleen, joints, &c. (see previous remarks about fig. 5.) The enlargement of the spleen in malarial fevers has an interesting relation, as I shall have to point out at some future time, to the amount of uric acid that can be retained in the body in this disease, and in other diseases in which this organ is enlarged. I have found the spleen, as above shown, to contain about 4·5 grs. per pound; so that obviously a spleen weighing 6 to 8 lbs. would contain 27—36 grs., and if this organ is alternately filled up and emptied in the alternations of fever and remissions, we shall be able to account for all the uric acid which is so often found in excess in some part of the body in these cases. Again, if we reflect that the holding back or retention of little more than 1 gr. a day, that is to say, if the formation plus the introduction of the 24 hours exceed the excretion of the same period by one grain (and it is easy on any given day to produce a retention to this extent with drugs) will furnish 1 oz. of uric acid in a year, we shall be at no loss to account for all that is ever met with in the body after death, whether in the joints, viscera, and tissues, or in the urinary passages in the form of calculi.

On the fall of temperature the alkalinity of the blood was increased, and it dissolved out and removed the uric acid from its places of deposit; if the urine had been examined at the same time, corresponding changes in the quantity of uric acid excreted would have been observed, and as I have already pointed out, the amount of urinary water and the rate and tension of the pulse would show concomitant alterations corresponding to the effects of the uric acid on the capillaries (see fig. 55).

In diseases of the liver, intestines and stomach, there was only uricacidæmia when they went along with anæmia. I should be inclined to read for anæmia wasting and debility, with their result a fall in the excretion of urea and acid, and a consequent fall in the acidity of the urine and increase in the alkalinity of the blood. Among heart diseases he observes that those had most uric acid in the blood in which the disease caused most cyanosis.

Again, he often found uric acid in the blood in diseases of the lungs and pleuræ, emphysema and exudations.

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He found it constantly present and in considerable quantity in five cases of pneumonia even during the febrile stage.

The explanation of these results in pneumonia which appear to be in opposition to my result will be gone into presently. The blood, in the single case of this disease I was able to examine, was drawn early in the acute stage of the disease, and it must be remembered that in my results with *post-mortem* blood I found an extremely large amount of uric acid in the blood of pneumonia cases.

None in six cases of rheumatic fever.

A very considerable quantity in kidney diseases of different forms, ten cases.

From these results he deduces the general statement that the blood contains much uric acid in all cases of primary and secondary anæmia;

That uric acid is present in the blood in considerable quantities in other diseases besides gout;

That uric acid does not take part in the acid intoxication of fever, since fever is unfavourable to the presence of uric acid in the blood;

That in dyspnœa and cyanosis the more the blood is overloaded with carbonic acid, the more uric acid it contains. Hence in pneumonia you may get uricacidæmia in spite of the fever.

And lastly, he concludes that it is plus in nephritis and anæmia, because the red cells are unable to further oxidise the uric acid, and hence everything that interferes with the oxygen-carrying power of the red cells causes excess of uric acid in the blood.

This sounds on the face of it a very plausible conclusion, but my researches on the excretion of uric acid throw, I think, considerable doubt on its validity, and we shall, I think, see eventually that all excess of uric acid in the blood is *the cause* of defective interchange between the blood and the tissues, and so of defective nutrition and combustion in general; and that the cause being removed the effects remain absent.

It has long been known that the excretion of uric acid is large in the morning when the acidity of the urine is low, in what Sir W. Roberts has named the "alkaline tide."

This has, I think, been generally regarded as due to a plus formation of uric acid during these hours; but I have shown that the excretion of uric acid, both in these hours and at other times of the day, can be altered in either direction. The natural plus excretion of the "alkaline tide" can either be increased very considerably, or diminished to a corresponding extent. If it is required

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to increase it, this can be done by first retaining a little uric acid in the body by acids given on the previous day, and then increasing the alkalinity next morning with a dose of alkali. If it is required to diminish it, this can be done directly by giving an acid to counteract the alkali of the "alkaline tide"; or more powerfully still, by removing all the most easily available uric acid stores on the previous day by giving a powerful solvent, as salicylate of soda, when the "alkaline tide" next morning will have nothing to act upon, and there will be no plus excretion of uric acid. I have given instances of all these results before, and any one who will take the trouble to give a few drugs and watch the results, may easily convince himself that the excretion of uric acid can be varied at pleasure in either direction.

It may be of interest if, in illustration of what I have been saying, I refer again to fig. 8. From this it may be seen that a dose of 15 grs. of the salicylate, taken three times a day for five days, produced on the first day it was taken a very large excretion of uric acid. Next day, the drug being continued as before, it fell down close to the urea again; then on the two following days (4 and 5 in the figure) it rose a little, but to nothing approaching the height of its rise on the first day (day 2 of figure). On day 6, the last day of salicylate, it came still nearer the urea; and on day 7, when salicylate was left off, it fell very far below the urea, and remained there, as my curves (not given in the figure) show, for the three following days.

All curves of uric acid excretion under salicylate show practically the same thing, and the same is seen in the excretion curve of acute rheumatism treated by this drug (see fig. 59), only that the quantities are greater. In all, the excretion reaches its highest point on the first or second day, and the same height is never again attained, however long the drug is continued. On the contrary, the excretion shows a tendency, with a few oscillations, to come down to the level of the urea and remain there; and if the drug is now stopped it at once falls far below the urea, and remains there for several days.

My explanation of these results is, that on the first day it is given, the salicylate meets with a considerable amount of uric acid in the joints, liver, spleen, &c., on which it is easily able to act; that as it gets this into solution and passes the greater part of it into the urine, it never on any subsequent day meets with so much uric acid on which it can act, hence the curve never rises so high again. On subsequent days a little is introduced or here and there comes within its range of action, but each day there is less and less

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left, so that the curve approaches the urea that is the level of formation.

As soon as the drug is withdrawn there is at once a retention of uric acid (day 7), replacing to some extent what has been removed from the organs and tissues by the solvent.

If on day 2 an alkali had been given in place of the salicylate, it would have produced a plus excretion of uric acid; but the same dose of alkali given on day 7 would have quite failed to raise the uric acid above the urea; the more powerful solvent salicylate has now removed so much uric acid that the alkali has nothing to act upon. It will now be understood that by giving drugs in this manner, and watching their effects from day to day, or, if need be, from hour to hour, it is no very difficult matter to alter the excretion of uric acid in any required direction.

The plus excretion of the "alkaline tide" is thus seen to be a single instance of a general rule which may be thus stated. All substances which increase the solubility of uric acid increase its excretion (provided there is some uric acid in the body for them to act upon); and conversely, all substances which diminish the solubility of uric acid diminish its excretion, and cause it to be kept back and retained in the body. If the normal plus excretion of uric acid in the "alkaline tide" was due to plus formation, why should the previous removal of uric acid diminish it, or why should the previous storing up of uric acid increase it?

I have given above my reasons for believing that every plus excretion of uric acid in the urine is simply the overflow from an excess of this substance in the blood, and that when there is a diminished excretion in the urine there is none, or almost none, in the blood. In other words, that the amount of uric acid in the urine in relation to the urea is the index of the amount in the blood, and that in altering the amount in the excretion we of necessity alter at the same time the amount in the circulating fluid.

The results published by Professor v. Jaksch will presently be seen to be simple instances of the action of the law of solubilities above stated.

From my point of view I can show that alkalies, phosphate of soda, and compounds of salicylic acid, increase the excretion of uric acid in the urine, and for a time also increase the amount of it in the blood. Conversely acids, iron, lead, and other substances mentioned before, diminish the solubility of uric acid, diminish its excretion in the urine and the amount of it in the blood. That acids, iron and lead interfere with the solubility of uric acid is well

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known, and lithia, as I have pointed out elsewhere,[1] though said to be a beautiful solvent of uric acid in a test tube, yet when given to the human subject by the mouth never reaches the uric acid at all, because it at once forms an insoluble compound with the phosphate of soda in the blood, thus removing from that fluid one of the natural solvents of uric acid, and diminishing its power of holding uric acid in solution; and in accordance with this, as I have pointed out, it diminishes the excretion of uric acid in the urine and the amount contained in the blood, and as a result of this it has the same effect on the rate and tension of the pulse, the flow of urine, and the circulation of the brain (as evidenced by the mental condition) that acids, iron, and lead have, though acids raise the acidity of the urine and diminish the alkalinity of the blood, and lithia lowers the acidity of the urine and increases the alkalinity of the blood; thus clearly showing that the pulse rate and tension and the circulation in the various organs mentioned are not directly affected by the drugs used, but only indirectly through their effects on the solubility of uric acid and the amount of this substance which the blood can hold in solution.

Under ordinary circumstances a dose of potash or soda will increase the excretion of uric acid in the urine, and will also increase the amount of uric acid in the blood; as a result of this, it will slow the pulse, raise the tension, and produce mental depression and scanty urine from its effect on the circulation of the brain and kidney respectively; but if all the available uric acid has been cleared out of the body by giving a salicylate for two or three days beforehand (see fig. 8), then a dose of soda or potash will produce no plus excretion of uric acid in the urine and no excess of it in the blood; and in accordance with this, none of the above-mentioned vascular phenomena will make their appearance, and the circulation in the brain and kidney will go on unhindered; thus proving beyond all doubt, that these vascular phenomena are due, as I have previously pointed out, not to the direct action of the drugs used, not to the greater or less alkalinity of the blood *per se*, but to the larger or smaller amount of uric acid which it is able to hold in solution. We shall see also in chapter viii. that the larger or smaller amount of uric acid in the blood determines the presence or absence of fatigue, and the rise or fall of urea as the result of exercise; and we have already seen (fig. 5) that it affects both the distribution and the production of heat.

[1] *Med. Chir. Trans.*, vol. lxxi., p. 287.

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I think, therefore, that the connection traced by Professor v. Jaksch between deficient oxidation and excess of uric acid in the blood is quite correct as regards the facts, only the explanation is probably a little different from that which he has given.

Dr. Peiper, whom v. Jaksch quotes, points out that the alkalinity of the blood is diminished in all fevers, except when they are complicated by dyspnœa and cyanosis.[1]

Now this is a most important exception, and on further investigation it will, I think, be seen that it furnishes us with an easy explanation of most of Professor v. Jaksch's facts.

It may be worth while to stop for a moment and enquire why dyspnœa and cyanosis, that is, deficient oxidation, should prevent the diminution of the alkalinity of the blood which commonly takes place in fever.

We have not very far to look for an explanation, for the word oxygen itself supplies one to hand, as its derivation, given in every work on chemistry, *ὀξυς*, acid, and *γενναω*, I produce, at once furnishes a clue.

It is extremely probable, one might almost say certain, that oxygen in the human body acts just as in the chemical laboratory, and when it oxidises certain substances produces certain compounds of an acid nature, and that form of motion which we call heat.

I know as a fact that when certain compounds of sulphur are given by the mouth, they themselves having a neutral reaction, there is soon seen a very marked rise in the acidity of the urine, as if a very strong dose of acid had been given, and this rise goes on for some little time (see fig. 11). Now, it seems to me that there can be scarcely any room for doubt that this is due to the oxidation of the sulphur with the formation of some acid.

And it is extremely probable that in the ordinary metabolism of the human body exactly the same thing occurs, that oxygen combines with certain elements in the food or tissues to form as in the laboratory heat and acids; in fever the same processes are carried to excess, and we have as their result a rise of body temperature and an increased formation of acids causing a rise in the acidity of the urine and a fall in the alkalinity of the blood (see also chapter iv.)

But if oxygen is deficient, if there is dyspnœa or cyanosis, the chemical changes are interfered with and the temperature does not rise so high, and there is a lessened formation of acid; hence, as

[1] Virchow's *Archiv.*, June, 1889, p. 337.

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pointed out by Dr. Peiper, the alkalinity of the blood is not diminished.

If then, with regard to the amount of uric acid found in the blood by Professor v. Jaksch, we read for deficient oxidation, *deficient formation of acids*, we are at once in a position to explain all his results; as the excess of uric acid which he finds in the blood in all conditions of diminished oxidation can at once be accounted for by my law of solubilities previously stated.

In ordinary fevers the increase of oxidation diminishes the alkalinity of the blood and reduces often to *nil* the amount of uric acid it can hold in solution; hence the results of Sir A. Garrod in acute rheumatism and the concordant results of Professor v. Jaksch and myself in fever and inflammation.

But if there is a deficiency of oxygen the acids are not formed, the alkalinity of the blood is not diminished—it may even be increased; and its solvent power for uric acid being thus undiminished or increased, it at once takes up a large amount in solution, and there is a corresponding increase in the amount passed in the urine.

As I have also pointed out, precisely the same changes in the amounts of uric acid in the urine and in the blood can be produced at will by giving alkalies and acids respectively.

There is, as I have said before, no reason to believe in the existence of an excessive formation of uric acid, and all fluctuations in excretion can be explained by its simple retention, so that what Sir A. Garrod said about lead (previous quotation) is probably true of all substances that affect the excretion of uric acid in the same way.

Practically, in the human body uric acid is always formed in a definite proportion to urea, about one grain of uric acid for 40 grains of urea; and I have given above some reasons for this statement. Sir A. Garrod[1] noted this fact, and sought to explain it by suggesting that certain cells in the kidney formed urea, and certain other cells, having a definite numerical relation to them formed uric acid; but I am inclined to believe that a satisfactory chemical explanation of the relative formation of these two substances may yet be forthcoming.

So that the whole of Professor v. Jaksch's results refer to excretion of uric acid, and have nothing to do with formation; and his extremely interesting observation on the relation between anæmia and excess of uric acid in the blood, which agrees so com-

[1] *Brit. Med. Journ.*, vol. i., 1883, p. 547.

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pletely with my own as regards the facts, is also made the foundation for an absolutely erroneous inference, for my researches further on show pretty clearly that he has exactly inverted the truth, and that, instead of the anæmia being through deficient oxidation, the cause of the excess of uric acid, the excess of uric acid is the cause of the anæmia.

Fig. 21 shows the effect of an iodide on the excretion of uric acid. On day 1 uric acid is high, and on day 2 it rises still further.

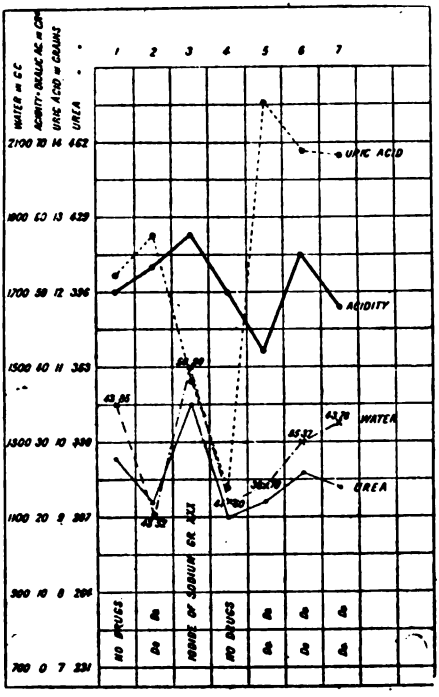

FIG. 21.—RETENTION OF URIC ACID PRODUCED BY AN IODIDE.

On day 3 gr. x. of iodide of sodium are taken three times, and uric acid falls and comes close to urea; and on day 4, though no more of the iodide is taken, it falls further and remains close to the urea. On the remaining days of the figure no drugs are taken, but on day 5, the effect of the iodide having now passed off, uric acid rises very high. This constitutes what I have spoken of as the rebound, and makes it probable that the low excretion of urate

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on days 3 and 4 was not due to its destruction or elimination in other forms, but to its retention in the body, the iodide making the blood for the time being a bad solvent of urates, so that they are retained in the liver, spleen, kidneys, and fibrous tissues, and when the effect of the iodide passes off they are again taken up by the blood from these organs and tissues and excreted in excess in the urine. A similar plus excretion of the rebound is seen after all substances which, like iodine, cause retention of uric acid. Those substances on the other hand which cause a plus excretion of uric acid, as alkalies, salicylates, &c., are followed by a great fall in urate excretion the day after they are left off (see figs. 7 and 8.)

On days 6 and 7 in this figure uric acid remains high and a long way above urea.

Note also that the usual relation of uric acid to acidity is broken through, for urate falls and remains low on the fourth, though acidity has fallen decidedly. On the fifth, however, the effect of the iodide passes off, and the fall of acidity allows of a plus excretion of urate; on the sixth acidity rises and urate falls somewhat, so that it has regained its normal relation to acidity.

See also the excretion of water, how it rises to 1,500 cc. on the third with the fall of urate down close to urea. On day 2 uric acid exceeds the relation to urea of 1—33 by nearly $3\frac{1}{2}$ grs., that is to say, on this day about $3\frac{1}{2}$ grs. of uric acid passed through the blood, the arterioles of the kidney and whole body were contracted or the capillaries obstructed by the urate, and hence the urinary water was scanty, only 1,100 cc. On day 3 the iodide produces its well-known diuresis, and this diuresis, like that of many other drugs which cause retention of uric acid, is due to its clearing uric acid out of the blood. On day 3 uric acid was above urea by only $\frac{1}{4}$ of a gr., therefore, only $\frac{1}{4}$ gr. passed through the blood, the capillaries were everywhere freed, the circulation through the kidneys was free, and the urinary water ran up to 1,500 cc.

In a paper on "The Iodides and their effects on arterial tension and the excretion of urates," *Transactions of the Royal Medical and Chirurgical Society*, vol. lxxvi., p. 113, I have pointed out that the relaxation of arterioles and the diuresis which the iodides produce are contemporaneous with a diminished excretion of uric acid in the urine, and I have further said that a large number of drugs and disease processes which similarly diminish the excretion of uric acid and clear it out of the blood produce also a relaxation of arterioles, or as I should now prefer to say, a freeing of capillaries, and a diuresis, and that arterial tension is influenced, not by the drugs,

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but by their effects on the solubility of uric acid and the amount of this substance present in the blood.

Copaiba is another drug whose power of causing diuresis is well known, and I would point to fig. 22, as showing that just as with iodides, of which we have been speaking, the increased excretion of water is contemporaneous with a fall in the excretion of uric acid, and we are bound therefore to consider whether its action is not due to its effects on the solubility and excretion of uric acid.

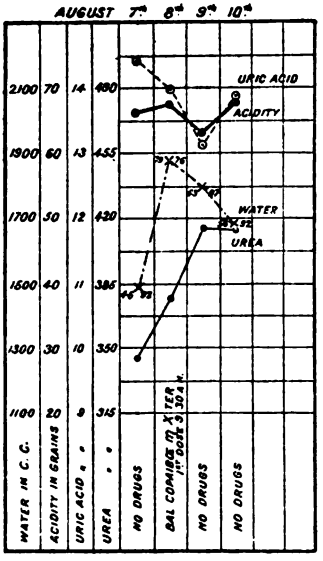

FIG. 22.—EFFECTS OF BALSAM OF COPAIBA ON THE EXCRETION OF URIC ACID AND WATER.

In this figure we see that on August 7, uric acid exceeded the relation to urea of 1 to 35 by nearly $4\frac{3}{4}$ grs., that is to say, $4\frac{3}{4}$ grs. passed through the blood. On this day the urine was rather scanty in the day hours, but this was made up for by an excretion of exactly double the amount in the night hours. On the 8th on which the copaiba was taken uric acid fell, and urea rose so that only $3\frac{1}{4}$ grs. passed through the blood, and with this we see that the water rises decidedly, being nearly twice as much in the day hours as on the 7th.

On the 9th, uric acid falls still further, and urea continues to rise so that only $1\frac{1}{4}$ grs. of uric acid passed through the blood, and

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with this the urinary water remains high, but the hourly excretion at night is again larger than that in the day hours.

On the 10th urea is stationary, while uric acid rises so that 2 grs. pass through the blood, and with this the water falls and the hourly excretion at night is nearly double that in the day.

We see, then, that on the 8th and 9th urinary water is high, and that this corresponds with a well marked fall in the quantity of uric acid passing through the blood on these days.

The diuresis produced by copaiba is therefore merely another illustration of the action of my law of excretions, that the urinary water varies from hour to hour and day to day inversely as the height of the uric acid, above urea, that is inversely with the amount of uric acid passing through the blood (see description of figs. 1, 2 and 3). We are less concerned with the manner in which copaiba interferes with the solubility and excretion of uric acid, than with the fact that it does so; but on looking at its composition one cannot help being struck with the large amount of acid (copaibic acid) it contains.

The rise of acidity on August 8 is small, especially as there is a pretty marked rise of urea; but it looks as if there must have been something to raise the acidity on the 8th, because it falls on the 9th in spite of a further and more marked rise of urea.

It is interesting also to note that several substances which produce similar effects, as tar, turpentine, cannabis indica, and guaiacum contain also very similar acids or acid resins; and I believe that a very large part of the physiological and therapeutic effects of the drugs just named, can be completely explained by their action on the solubility and excretion of uric acid which controls the circulation throughout the body. With reference to guaiacum I would refer to my remarks in the debate on Sir A. Garrod's paper on this drug, at the Royal Medical and Chirurgical Society (see Proceedings, 26th May, 1896, also *Lancet*, 1896, vol. i. p. 1494), and in the above debate Dr. Norman Moore mentioned the interesting fact that in the 17th century guaiacum was considered as the best remedy for tertiary syphilis; it would certainly tend to clear the blood of uric acid, and free the capillary circulation just as do the iodides used in these days.

We now come to uric acid itself, and a large group of substances which are almost chemically identical with it.

Uric acid and all these related substances have several important effects which are common to them all, and the chief of these is the fact that they all interfere with their own solubility

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in the blood; they not only do not remain in solution in the blood themselves, but they prevent any other similar compounds that may be otherwise present in the blood stream from remaining in solution.

And they probably produce this effect by acting like acids or acid salts, such as the nitrites, sulphites, salts of the mineral, and other acids of which we have spoken, so that when they get into the blood they take alkali from the normal phosphates of the blood and convert them into acid phosphates, which, as we have seen, are not solvents of uric acid.

The solvent powers of the blood for uric acid are thus diminished by them, with the result that the blood stream is at once more or less completely cleared of this substance, and the whole of their physiological and pathological effects depend upon this action.

The substances which thus at once clear themselves and their relatives out of the blood stream, pass, as we have seen reason to believe, into the parenchyma of the liver, spleen, kidneys, and many fibrous tissues throughout the body; but in the natural course of events, perhaps introduced in food a fresh supply of alkali gets into the blood, the acid phosphates again become normal phosphates, and the solvent powers of the blood for uric acid and its congeners are restored.

The blood now acts on the uric acid previously driven out of it into the above named tissues and organs, gets a certain quantity of it into solution, and keeps it in solution till it is all excreted by the kidney, or till a fresh introduction of acids in some form drives it again out of the circulation into the tissues.

The urine is thus an absolute index of what is going on in the blood, and we can now completely understand why the excretion of uric acid varies from hour to hour and day to day inversely with the acidity of the urine.

I notice that Dr. J. Fawcett in the last vol. of Guy's Hospital Reports (1896, vol. 52, p. 140) objects to my saying that uric acid varies inversely as the acidity of the urine, and also that the acidity of the urine is sometimes due to uric acid, and he thinks this last is an unfair deduction.

But I must explain that the inverse relation between the excretion of uric acid and of acid in the urine is only strictly true in physiological conditions and where the daily introduction of uric acid is moderate and does not vary much; thus, if 10 grs. are taken in to-day, 15 to-morrow, and only 5 the next day, there will

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be large variations both in acidity and in excretion, and they will not always vary in the rule.

Again, if we consider for a moment that the excretion of uric acid in the urine is the resultant of two factors :—(1) The amount available ; and (2), its solubility in the blood ; we see at once that as the acidity of the urine varies for the most part with only one of these factors (*i.e.*, the alkalinity of the blood and its solvent power for uric acid), unless the other factor (the amount available or the introduction) is kept fairly constant, there will be exceptions to the rule.

Thus I could increase my excretion of uric acid to-morrow by taking an alkali, but if I also swallowed some extra uric acid along with the alkali I should have a still larger excretion than if I only took the alkali alone.

My own physiological results were obtained on a practically constant diet, with a fairly constant and very small daily introduction of uric acid, and so that the amount available for solution varied but little ; but even here the results are occasionally put out by introduction, especially in the curves obtained some years ago, before I knew all I have since learned about introduction in various substances.

In pathology the same rule holds for the most part, but there are one or two exceptions such as gout and rheumatism, when the uric acid has, so to speak, an additional outlet, being taken up and deposited in the fibrous tissues that have become the seat of chronic irritation.

Here any uric acid in solution in the blood is apt to be attracted to and caught up by the urates already in the seat of gouty irritation (just as uric acid on a filter soon clears all the uric acid out of the urine, that is poured over it), hence in gout it is not brought to or excreted by the kidneys to such an extent as one might expect from any given fall in the acidity of the urine.

Hence the well-known alternation of gout with melancholia, and migraine with rheumatism when urates are being retained in the fibrous tissues and joints the blood contains relatively little, so that high blood pressure and its effects are absent.

During the continuance of the gouty condition that tophus in the big toe is being daily increased by the addition of all the uric acid that is brought to it in the blood ; but the rest of the blood is thus kept poorer in uric acid, so that the excretion from the kidneys is less than the acidity of the urine might lead us to expect, and there is no high blood pressure and no melancholia.

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Again, clinically, nothing is more common than to hear a patient say that she suffered much from rheumatism a year or so ago, but that lately the rheumatism has been better and the headaches much worse. This means that an increase of debility or other cause of a rise in the alkalinity of the blood has reversed the above process, and urates are now being taken up from the fibrous tissues, in place of being deposited in them.

We can now understand why Dr. Fawcett could not imitate my physiological results with alkalies when working on cases of gout, and he also further complicated matters by giving foods (eggs, fish, and tea, and occasionally full diet) which varied somewhat from day to day, and introduced various amounts of xanthins, to which apparently he paid no attention.

With salicylate of soda, however, he was able to get results much more nearly resembling mine, for the salicylate was at once able to dissolve the uric acid out of the gouty joints and fibrous tissues, and bring it in a steady stream to the kidneys for excretion (see action of salicylates, chap. ii.)

Another exception to the physiological rule of excretion is seen in epilepsy; here with the large excretion of uric acid that follows the fit there is a very marked rise of urinary acidity, which is in contrast with any ordinary rise of urinary acidity in not being accompanied by a rise of urea, the two curves generally rising and falling together in about the relation of 1 of acidity for 6 of urea. (see chap. ii.)

But in epilepsy the urea does not generally rise after the fit (see cases in chap. vii.), it more often falls, hence we cannot look to the ordinary source for the explanation of the rise of acidity of the urine.

I have accordingly suggested that the rise of urinary acidity that follows the fits of epilepsy is due to the great excess of uric acid which that urine contains, and I think that this rise of urinary acidity apart from urea is no proof that the alkalinity of the blood is diminished, for if it had been so the large excretion of uric acid would not have gone on.

Dr. Fawcett regards this as an unfair deduction, but I have stated the facts as clearly as I can, and it is open for him or anyone else to give them a better explanation.

While speaking of Dr. Fawcett's results, I may mention that he was unable to see that colchicum lowered the acidity of the urine; but then I notice that he used the vinum, and in rather small doses; and sherry, as we shall see in fig. 54, distinctly raises the

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acidity of the urine, and would therefore tend to counteract the effects of the colchicum. In my experiments with colchicum I used tr. colch. sem., the alcohol in which would at least do nothing to counteract the effects of the colchicum on the acidity of the urine.

Dr. Fawcett also thought he saw some exceptions to my rule as to the inverse relation between water and uric acid in excretion, but his remarks raised in my mind a doubt whether he had read carefully my remarks on this subject with reference to fig. 3, and in any case with the very complex excretions he would get dealing at one and the same time with pathology, drug action, and varying food and introduction, I should not expect the rule to come out clearly.

But to return: the primary effect of taking any of these substances, is to clear the blood of uric acid, and nearly all its other immediate effects are the results of the circulatory changes which this produces; on the other hand, their secondary effect is to flood the blood with uric acid, and this again accounts for all the other secondary effects.

Fig 23 shows as we shall see both these series of effects very well. I shall now mention the chief substances in this group with their chemical composition, and then pass on to describe in detail the physiological effects of a few of the most important ones.

Uric acid = $C_5.H_4.N_4.O_3$.
Xanthin = $C_5.H_4.N_4.O_2$.
Hypoxanthin = $C_5.H_4.N_4.O$.
Guanin = $C_5.H_5.N_5.O$.
Kreatin = $C_4.H_9.N_3.O_2$.
Kreatinin = $C_4.H_7.N_3.O$.
Glycocoll = $C_2.H_5.N.O_2$.
Theïn or Caffein = $C_8.H_{10}.N_4.O_2$.
Theobromin = $C_7.H_8.N_4.O_2$.
Other vegetable alkaloids of similar composition.
Ptomaïnes.

I shall have to point out that as regards physiology and pathology it makes absolutely no difference whether we swallow a grain of uric acid, xanthin, hypoxanthin, theïn, caffein, or theobromin; all alike produce as a primary effect clearance of uric acid from the blood with free capillaries and general stimulation of metabolism and nutrition; all alike have also a secondary action or rebound when the uric acid again passes into solution in the blood with

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obstructed capillaries and general depression of nutrition and metabolism.

What we know of several other vegetable alkaloids and their physiological effects points strongly to their acting in exactly the same way, and what we know about ptomaines makes it worth while to bear in mind the possibility that, such part of their action as resembles that of the above substances, may be produced in exactly the same way.

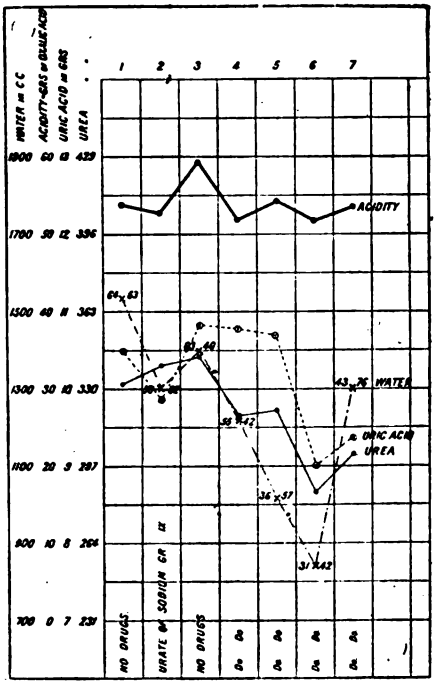

FIG. 23.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING URATE OF SODIUM.

Guanin is a very similar substance, and glycocoll I have previously spoken of as uniting with benzoic acid to form hippuric acid, and with salicylic acid to form salicyluric acid (see salicyluric acid, p. 37); it also under certain conditions unites with ten parts of urea to form uric acid.

The whole of these substances thus stand together in a natural group which from my point of view is of enormous importance.

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Now fig. 23 shows the effect of taking urate of sodium (grs. 9) by the mouth, and it apparently produces a rise in the excretion of uric acid, not on the day it was taken, but on the first, second and third day after the dose. Its first effect is to clear the blood of uric acid, and with this the excretion of uric acid falls below urea on day 2. The rise of acidity on day 3 is partly the result of the action of the urate on the phosphates of the blood before mentioned, and partly also due to the increased metabolism which clearing the blood of uric acid produces, and this again accounts for the rise of urea on days 2 and 3. But the increased metabolism comes to an end, the urea falls and the acidity with it, and now the uric acid which was stored up on day 2 is got into solution in the blood and passed out in some excess in the urine during the rest of the figure. Precisely the same thing occurs if uric acid is taken in place of a urate, but here again, on one of the following days, acidity falls, and uric acid rises and remains high for several days more or less in proportion to the dose taken.

If, however, acidity runs at a very high level, as in a person who eats much meat and drinks wine, taking uric acid or urates by the mouth may apparently produce no effect whatever on the excretion of uric acid; for the excretion of uric acid is dependent on its solubility in the blood, and where the conditions are unfavourable for this solubility it remains in the body instead of passing through the blood into the urine. In this figure it was the fall of acidity on day 4 that made the plus excretion of urate on this and the following day possible, but had there been no urate introduced this fall in acidity might not have been followed by a rise in its excretion.

If, on the other hand, the blood is kept in a condition to hold uric acid in solution by supplying it with alkalies or salicylates beforehand, the uric acid or urates taken by the mouth pass almost at once through the blood into the urine, and by repeating and varying the dose, it is easy to show that the excretion is proportional to the amount ingested. Thus in the *Journal of Physiology* (vol. xv., p. 167) to which I must refer for further figures and details, I have shown that while a given dose of salicylate of soda produced in five days, under ordinary circumstances, an excretion of uric acid which exceeded the relation to urea of 1 to 33 by 11¼ grs., a similar course of salicylate taken on other five days along with 12 grs. of uric acid produced an excretion of 20¼ grs. above the relation to urea of 1—33.

It does not seem to me that there is any reason to doubt that the extra 9 grs. excreted on the latter occasion came from the quantity

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ingested, and that if the experiment had been continued a day or two longer the whole of the 12 grs. would have been excreted.

Fig. 24 shows the effect of two dinners consisting of soup, fish and meat, on two consecutive days on the excretion of uric acid. On the 11th uric acid exceeded the relation to urea of 1—35 by about 1 gr., on the 12th, the day of the first dinner, it exceeded it

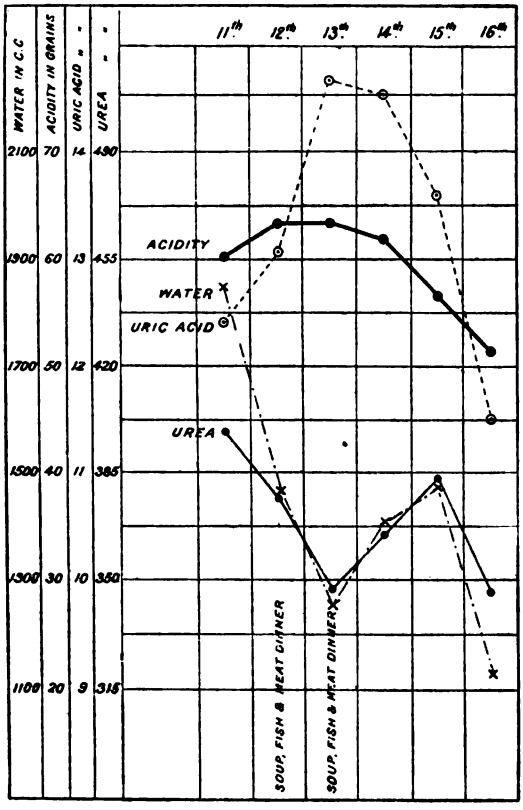

FIG. 24.—EFFECT ON THE EXCRETION OF URIC ACID OF SOUP, FISH AND MEAT.

by 2¼ grs., on the 13th, the day of the second dinner, by 4¾ grs., on the 14th by 4 grs., on the 15th by 2¾ grs., and on the 16th, the last day of the figure, by 1½ grs.

It appears, then, that the effect of these two dinners was to introduce into the body and pass through the blood some 15 grs.

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of uric acid, or if we take off 1 gr. for each of the last five days in the figure on the supposition that as uric acid was above urea by 1 gr. on the 11th, it might have exceeded urea by this amount on the following days even if no soup, fish or meat had been taken, we still get 10 grs. as the introduction of the two dinners, or 5 grs. for each.

In a paper in the *British Medical Journal*, 1894, vol. ii., on the "Direct Introduction of Uric Acid into the Body, its Bearing on the Prevention and Treatment of Disease," I have pointed out that, judging from the quantities of various substances taken, and the quantities of uric acid or xanthins they contain, a man may easily introduce nearly 2 grs. of uric acid with an ordinary dinner, and as we shall see further in chapter xvii., the percentages of uric acid from which this is calculated are probably decidedly under the truth, so that the introduction of 4-5 grs. with a carnivorous dinner is by no means extraordinary.

It appears, then, from this figure that uric acid passed almost directly into the blood and urine, and that there was no first stage of stimulation due to the blood being cleared of uric acid. And this illustrates a very important point, namely, that uric acid will produce one or other of two opposite effects according as it is introduced, with conditions which are favourable to its solubility in the blood, or the reverse.

Now in fig. 24 the conditions were distinctly favourable to its solubility in the blood, because as I generally take neither meat nor wine the alkalinity of my blood rules high, and uric acid was already in some excess in that fluid on the day before the first dinner. The first dinner, therefore, failed to stimulate, it failed to overcome the depressing effect of the uric acid already in the blood, it failed, therefore, to raise either urea or acidity, and the uric acid it introduced passed almost at once into the blood and added its depressing effects on circulation, nutrition and metabolism to those of the uric acid previously there.

On the 13th almost the same thing occurred; there was again a failure of stimulation and a further fall of urea, and again the uric acid introduced, passed almost at once into the blood and added to the general depression. The rise of acidity in this figure is very slight, and was very probably due to the rise of urinary acidity which excess of uric acid produces (see p. 37 and also chapter vii.), rather than to any real fall in the alkalinity of the blood. But those who eat meat two or three times a day, must not expect that they will be able to introduce uric acid

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into their blood in the direct manner shown in this figure; with higher acidity which they are certain to have so long as they keep well, the uric acid introduced will pass much more slowly into solution and be much more gradually excreted; a dinner of this kind will act as a stimulant, they will feel better and stronger and happier for it, and nothing will persuade them that they are doing themselves any harm by taking it. And so long as they keep well, they have decidedly the best of it, and can point triumphantly to very good results; it is true that they are continually introducing considerable quantities of uric acid, which remain in the body and may produce now and again more or less decided reminders of their presence in the shape of gout or rheumatism; but so long as the blood is kept clear or moderately clear of uric acid by continued stimulation, there is no great harm done, and they may suffer neither from gout on the one hand nor high blood pressure on the other.

Unfortunately, however, in the natural course of events as old age comes on, nutrition begins to fail, and further stimulation becomes more and more difficult, then alcohol, morphine, and cocaine are perhaps called in one after another to help to keep the fires going brightly; at first they succeed; later, like everything else, and even in large doses, they fail, and then comes the final disaster.

Urea and acidity fall down and down for the last time, and with this the long pent-up store of urates breaks its dams and rushes into the circulation with an overwhelming flood which completes the ruin.

Circulation, nutrition, and function are soon rendered nearly impossible, and the physiological wreck has a chance of destruction by some of the most terrible effects of the most severe uricacidæmia, as we shall see in the following chapters.

If it escapes the ever threatening rocks of cerebral hæmorrhage, it may drift onward through some years of the discomfort and misery of high blood-pressure and chronic Bright's disease, to end in uræmia on the one hand or heart-failure on the other.

Long before this stage has been reached, however, it will be quite obvious to onlookers that the meat-eater has got far the worst of the argument, and will presently have to pay a terrible price for his stimulants. Figs. 23 and 24 show what his meat does for him, and how it does it.

Fig. 25 shows in the same way as the previous figures the effects of taking meat extracts. On the 4th uric acid is below urea, urinary

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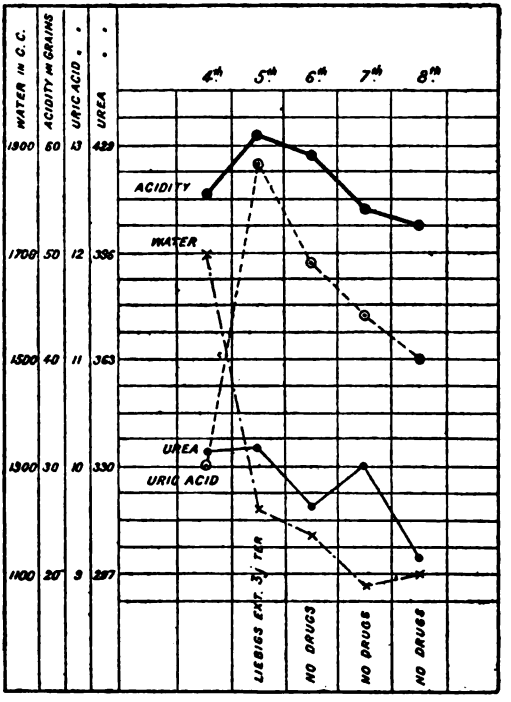
water is consequently high, and acidity stands about 55 grs.; on the 5th 3 drachms of Liebig's extract are taken in the course of the day, and the effect is that urea remains steady, uric acid rises quickly and decidedly, and water comes down equally decidedly, while acidity rises a little above 60 grs.

Here again, just as in fig. 24, the rise of acidity was probably due to the increased quantity of uric acid in the urine, and does



IG. 25.—EFFECT ON THE EXCRETION OF URIC ACID OF LIEBIG'S EXTRACT OF MEAT.

not show any diminished alkalinity of the blood, or the uric acid would not have been so freely excreted.

The rest of the figure merely shows that uric acid comes gradually down, there being no further introduction, that acidity falls more or less in parallel with it, and that urea falls also, part of its fall being, no doubt, due to the diminished metabolism which excess of uric acid in the blood produces (see chapter viii.), and last but

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not least, the water remains low the whole time the uric acid is high, thus again proving in the most absolute manner the obstruction of the capillaries of the kidney by the excess of uric acid in the blood.

Will anyone, after looking at these figures, dare to tell me that I cannot control from hour to hour or day to day the excretion of water from the kidney, or for that matter the circulation, function and nutrition of every organ and tissue of the body?

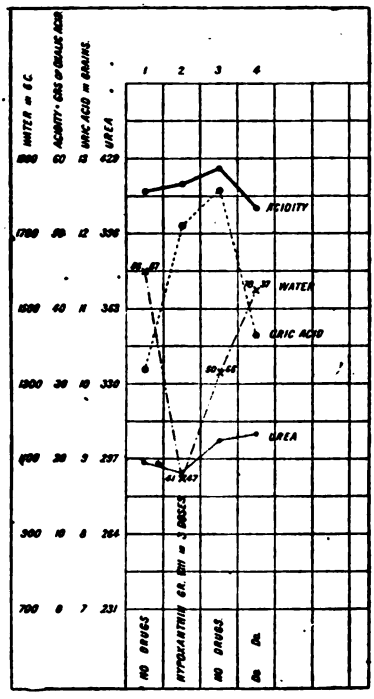

FIG. 26.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING HYPOXANTHIN.

We shall see further on that what controls the flow of water from the kidney controls also its exhalation from the lungs, and controls also digestion and all its excretions.

Fig. 26 shows the effect of 8 grs of hypoxanthin taken on day 2, and it appears to increase very markedly the excretion of uric acid which rises on days 2 and 3 in spite of a slight rise of acidity,

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and falls again on day 4 in spite of a fall of acidity. Note also the inverse relation of the urinary water which falls on days 2 and 3 with high uric acid, and rises again on day 4 as uric acid comes down.

What I have just said about the previous figures will apply almost word for word here; the hypoxanthin does not appear to increase the urea, and so far as acidity rises, this is again probably

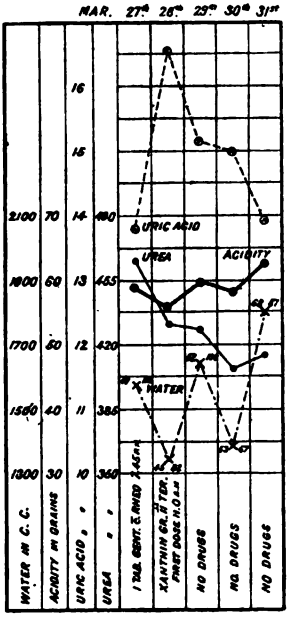

FIG. 27.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING XANTHIN.

due merely to the excess of uric acid in the urine and not to any change in the reaction of the blood.

It thus appears probable that the metabolism of the human body makes short work of the slight chemical differences between members of the xanthin group, and passes the greater part of them through the blood and into the urine as uric acid.[1] And one very important consideration forces itself in here, though I shall have to return to it again later on, namely, that if members of the xanthin group are thus converted into and must practically be reckoned as

[1] See also Lea, "Chemical Basis of the Animal Body," p. 182.

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uric acid, the estimation of the uric acid present in any food substance gives only an imperfect record of the amount of uric acid it may introduce into the body; for the xanthin and hypoxanthin remain unestimated to a considerable extent. The table, therefore, which I give of the amount of uric acid found in various food substances must be taken only as showing a part of the uric acid which these substances may introduce into the body, and important substances should be put to the more valuable physiological test of taking known quantities by the mouth, and estimating the increased excretion of uric acid produced as in the figures I am now describing. (See chs. i. and xvii.)

Fig. 27 shows the almost identical effects of swallowing a few grains of xanthin. Acidity is below 60 gs. a day, and the conditions are favourable to the solubility of uric acid in the blood, it is consequently nearly half a grain above urea on the 27th. On the 28th 6 grs. of xanthin are taken and uric acid rises sharply to about 4 grs. above urea and comes down rapidly on the 29th, and more gradually on the following days. Urea falls from the beginning to the end of the figure very much as it does in fig. 25, and probably for the same reasons.

Fig. 28 shows the effect of a dose of 10 grs. of citrate of caffeine taken on day 2, namely, a marked and immediate rise in the excretion of uric acid, which remains high above urea on all the subsequent days of the figure.

On day 1 uric acid exceeds urea by about 1½ grs.; on day 2 it exceeds it by more than 4 grs.; on day 3 by more than 5; on day 4 by 3 grs., and so on.

Here then we have another member of the xanthin group (for caffeine is, chemically, trimethyl xanthin—Lea, "Chemical Basis of the Animal Body," p. 175), which taken by the mouth markedly increases the excretion of uric acid, and the amount of that substance passing through the blood. And this result is, I believe, absolutely constant, for as will appear presently I have been able, by administering caffeine, to produce pathological changes in the blood similar to those produced by uric acid when taken in other forms.

An important corollary follows from this figure also, namely, that all vegetable alkaloids similar to caffeine, and which are chemically ureids or xanthins, must be regarded as possible introducers of uric acid into the body, and I have already mentioned this in chapter ii. in reference to the effect of quinine and strychnia.

Fig. 29 shows the effect of eating a sheep's thyroid gland, and

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this also apparently produces on the first, second and third days after its ingestion some plus excretion of uric acid.

The first effect of taking the thyroid was a very marked diuresis: the first dose of the gland was taken at 1.30 p.m., and it did not greatly affect the urine of the day which was 44 cc. per hour, but in the night following it ran up to 138 cc. per hour.

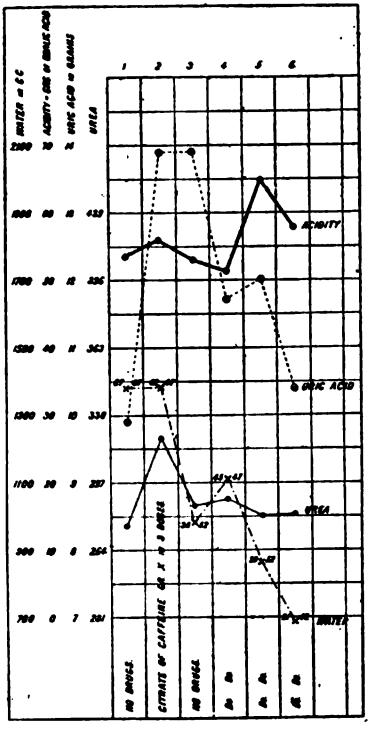

FIG. 28.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING CITRATE OF CAFFEINE.

Note that with this big diuresis there was a rise of acidity and urea, and that the uric acid exceeded the urea by almost nothing, that is to say, there was no uric acid passing through the blood.

Here we have shown in a very marked manner the primary stimulating effect of thyroid gland or extract; the secondary depressing effect was evident on day 4, and would have been still more evident on day 5, but for the drugs which had to be taken to make it possible for me to work.

Bear in mind also that acids, mercury, iodides, iron, lead, and a

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host of other drugs which clear uric acid out of the blood, will produce a similar rise of urea and a similar diuresis.

The sequence of causation in the case of this figure was probably somewhat as follows:—Eating the thyroid gland introduced certain nitrogenous substances and certain acids or acid salts; these produced a rise of urea and of acidity; this latter cleared uric acid out of the blood and freed the capillaries. With this freedom of

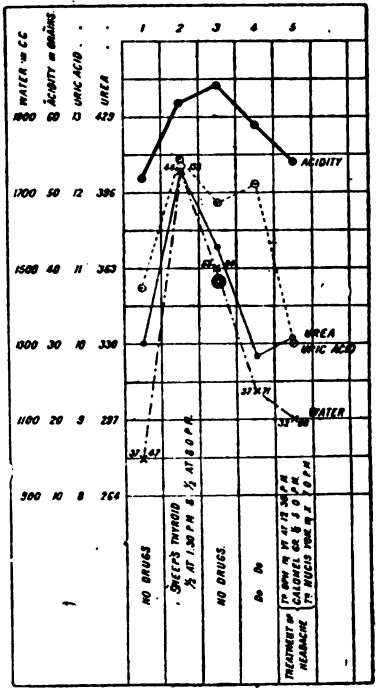

FIG. 29.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING A SHEEP'S THYROID.

capillaries went a general quickening of metabolism, and a further rise of urea and acidity, and the relaxation of the kidney arterioles allowed of a profuse diuresis because the water had been scanty on day 1, and fluid had been accumulating in the body.

On day 3 uric acid exceeded urea by ½ gr., and on day 4 by more than 4 grs., and it would no doubt also have exceeded it on day 5, but on the morning of this day there was considerable headache, and drugs which brought down the uric acid had to be taken to cure it.

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Note the large excretion of water on day 2 when uric acid is close to urea, and none passed through the blood, and its steady fall on subsequent days when uric acid rose, and also the extremely scanty water in the day hours of day 5, when there was a headache, and no doubt an excess of uric acid in the blood though the minus excretion produced by the drugs brought down the level for the whole twenty-four hours; but here the water tells us in which hours the uric acid was scanty and in which profuse. I notice also in a recent paper in the *British Medical Journal* (1897, vol. i., p. 196) it is stated that the most active constituent of thyroid gland is a compound of iodine (iodo-thyrin or thyro-iodin) contained in the colloid material, and this is most interesting, as I have just mentioned the iodides a few lines above as resembling it in their action. If this is so then the action of thyroid gland may be retention of uric acid, as shown in day 2 of fig. 29, followed by a rebound and plus excretion on days 3, 4, and 5, which exactly resembles the action of anyone of the group of drugs mentioned. But I should also have very little doubt that at least part of its effects are due to the nitrogenous extractives, which probably directly increased the excretion of uric acid on days 3, 4, and 5, and in which it is well known that these glands are rich (see Professor Foster's "Text Book of Physiology," ed. v., p. 762). And as we shall see presently in patients treated with these glands or their extracts, we soon get strong symptomatic evidence of the passage of an excess of uric acid through the blood, exactly as we do when uric acid is taken in other forms (see ch. xii.), and in my experience, after patients have been taking thyroid for a long time, they often suffer from periods of depression both of mind and body, these being, no doubt, contemporaneous with the passage through the blood of some of the excess of uric acid they have been introducing, but partly also due to a rebound after the action of the above iodine compound. We shall also see that the administration of thyroid extract affects the composition of the blood and precipitates attacks of angina or of epilepsy, just as in fig. 29 it produced (migraine) uric acid headache in myself, and that it acts in all these cases to a considerable extent in the same way as uric acid or any member of the xanthin group would do.

I may mention also here that others have noted a large excretion of uric acid in the urine during thyroid treatment, and have also seen some tendency to syncope while taking it,[1] which bears on what

[1] *Lancet*, 1896, vol. i., p. 1,446.

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I shall have to say presently on this subject in chapter viii. Mordhorst also refers in his paper in *Zeitsch. fur Klin. Med.*, to be mentioned in chapter v., to the fact that eating calf's thymus greatly increases the excretion of uric acid both in the gouty and the healthy, and thymus is very similar both to the thyroid and to the spleen as to the extractives it contains.

Several of the drugs of which I have been speaking and attributing their effects to their action on uric acid, are supposed to have some direct action on the heart or vessels, or both, or to influence certain centres in the brain and cord.

But a large part of this is admittedly mere hypothesis, and we must beware of taking it as representing a proved fact.

I by no means wish to assert that they have not these actions on the vessels and nerve centres, my facts will not carry me nearly so far as that, and I have no intention of going beyond them even by the fraction of an inch.

But the fact that we do not know everything is no reason why we should not observe carefully and argue logically as to the results of our observations.

To say, for instance, that small doses of opium in producing mental stimulation and well being act direct on the vessels or nerve tissues, is I think to talk nonsense and make two causes for one effect when one will suffice.

Opium, as I have shown, clears the blood of uric acid, which frees the capillaries all over the body, and alters the circulation from the crown of the head to the sole of the foot.

The altered cerebral function is either due to the altered circulation or it is not. If it is not, then why does every one of the long list of drugs mentioned above as clearing the blood of uric acid, and lowering the blood pressure, produce the same or similar effects on the cerebral function?

Is it likely that such drugs as copper, zinc, mercury, silver, lithia, acids and opium all affect the vessels or the nerve substance in the same way, or is their action due to that which alone is common to them all—their effect on the solubility of uric acid in the blood, and so on the circulation?

When any of these drugs produce results which differ absolutely from those produced by all the drugs which have a common action with them on uric acid, then some other explanation of their action must be found, but I am at present only concerned with their common action.

As regards opium, I have shown that if it is given when there is

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diarrhœa, or when the alkalinity of the blood is very high, it will have difficulty in reducing the alkalinity of the blood and affecting the solubility of uric acid, and under these circumstances its usual effects upon cerebral function, as also upon muscle function, and the fatigue it gives rise to, will be remarkable by their more or less complete absence; but when opium has thus failed, a drug such as mercury which clears the blood of uric acid by the direct formation of an insoluble compound with it, and is therefore independent of alkalinity and acidity, will succeed (see fatigue, ch. viii.).

All the drugs just mentioned, and many more that clear the blood of uric acid and alter the circulation of the whole body, affect not the cerebral function merely but the action of every gland and tissue in the body, thus increasing the formation and excretion of urea, but if their action on uric acid is prevented, then other effects fail to appear.

Thus salicylates cause diuresis, but not while uric acid is high, only when it is coming down on the second or third day of their action; while uric acid is high, urinary water is scanty. On the other hand, drugs which clear the blood of uric acid at once produce diuresis in a few hours.

It is again, I think, absurd to say that any of the drugs I have spoken of produce diuresis by acting on the renal epithelium.

If it is said that they act on the renal vessels, and not only on the renal vessels, but on all the other vessels of the body at the same time, I should offer no objection.

But to say that the substances belonging to this large group (only a few of which I have mentioned and given figures of) which have the power of diminishing the excretion of uric acid in the urine and clearing the blood of it, produce diuresis by acting on the renal epithelium, mental brilliancy and well being by acting on the nerve centres, increased flow of saliva by acting on the salivary epithelium, and of other excretions by acting on the cells of the stomach, intestines, liver and skin, increase of urea by acting on muscle fibre, and increase of expired water by acting on the pulmonary epithelium, and to ignore while we say this that the whole of these substances free the capillaries, lower the blood pressure, and so affect the circulation from end to end of the body and through all its tissues, is to talk the most absolute nonsense, to make the straight crooked, and the simple complex.

In the case of any single one of these substances which has the power of diminishing the excretion of uric acid and as a result of this (for it occurs constantly in physiology) increasing the excretion

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of water, it is easy to show that it increases not only the urine, but also the sweat, saliva, and all digestive secretions and functions, increases the water given off from the lungs, raises the temperature of the skin and extremities, and increases the formation of urea, thus dominating the phenomena of fatigue; and that all this is contemporaneous with a general freeing of capillaries and a fall of blood pressure, and that everything that produces these two last will also produce all the other effects.

In fig. 22 we see the rise of water and also the rise of urea, and similarly in fig. 21 there is a rise of urea as well as a rise of water when uric acid is brought down by iodides; a similar rise of water, contemporaneous with the clearance of the blood of uric acid and the rapid improvement of the blood decimal, is seen in the case of the patient who took iodide of mercury for chlorosis (fig. 48).

We shall see also in many other places that this same iodide of mercury is perhaps the most powerful drug we have, and the one on which we can most depend to clear the blood of uric acid, and counteract most of its effects in the causation of disease.

But even this drug will fail, and may fail ignominiously, if it causes salivation and gastro-intestinal irritation and diarrhœa, for these troubles always depress urea and acidity, and increase the alkalinity of the blood, and they will also diminish the absorption of the iodide, and under these circumstances the uricacidæmia and its effects will continue in spite of the drug, and you must now get the stomach and intestines into proper order before you will have any power to diminish the excretion of uric acid with drugs.

The primary stimulant action of uric acid and its congeners being thus in evidence, and it being also clearly proved that this is due to their interfering for a time with the solubility of uric acid in the blood, we are in a position to explain completely the primary stimulating effects of tea, coffee, cocoa, guarana, beef-tea, meat extracts, soups and thyroid extract, also the use of such things as pigeon's dung in ancient prescriptions, and a draught of child's urine as a stimulant by some nations at the present day.

It is a point of no little interest that these stimulating effects are in all cases due to one and the same chemical substance, and are produced in exactly the same way, and that this is also followed later on by depression, which requires further stimulation to remove it.

I am indebted to my friend, Mr. H. B. Meakin, formerly house surgeon and house physician at the Metropolitan Hospital, for the interesting information that in Morocco the popular remedy for

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severe fright in a child is a drink of urine, preferably that of a virgin; I will merely remark that if by a virgin is meant a young girl recently arrived at puberty, her urine would probably contain more uric acid then than at any other period of her life (see fig. 51).

I am also indebted to Dr. Rushton Parker for a reference to a paper by Dr. R. Neale in "Food and Sanitation," June, 1894, p. 195, in which he says, "In South America the urine of little boys is spoken of highly as a stimulant in malignant small-pox.

"Among the Chinese and Malays of Batavia urine is very freely used. One of the worst cases of epistaxis ceased after a pint of fresh urine was drunk, although it had for 36 hours or more resisted every form of European medicine. This was by no means an unusual result of the use of urine, as I was told by many of the natives. As a stimulant and general pick-up I have often seen a glass of child's or young girl's urine tossed off with great gusto, and apparent benefit. Dr. Hastings' report of the value of the excreta of reptiles in 1862, in the treatment of phthisis, will also be fresh in the recollection of the older members of the profession."

As regards the epistaxis, the urine had no doubt exactly the same effect as the iodide of mercury, of the value of which in other forms of hæmhorrhage I shall have to speak presently, *i.e.*, it cleared the blood of uric acid, and lowered the blood pressure; and reptiles' excreta in phthisis act in the same way as meat diet and other things of which I shall have to speak in chapter ix.

I would also remark in passing, that fright is a powerful depressant, and generally upsets digestion and metabolism, producing uricacidæmia (hence its common connection with the onset of chorea, see chapter xvi.) and a draught of urine or a dose of uric acid would, as some of the preceding figures show, be a very good way of clearing the blood of uric acid and putting an end to the depressing effects of fright; almost any of the above-mentioned stimulants in daily use would do as well, but possibly in Morocco urine is more easy to obtain than most of the others.

These figures, then, practically show that uric acid and many substances chemically related to it, as the xanthins, alkaloids and ptomaïnes, when taken by the mouth whether in food or as an addition to food, pass into the blood, and, when the conditions in that fluid are favourable to their solubility, remain there till they are excreted in the urine; that they are not to any appreciable extent converted (as was supposed) into urea; that the rise of urea which these substances produce is secondary to the rise of acidity which they also produce; and that other acids which introduce

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no nitrogen into the body produce a similar rise in the excretion of urea.

From these facts I think we may draw a few general conclusions.

First, that the amount of uric acid in the blood of man, and probably of animals also, is not a mere matter of chance, but is always subject to certain definite rules, which to my mind can be summed up by saying that the amount of uric acid in the blood is proportional to the solvent power of that fluid, and its contained salts for uric acid and its salts. Increase of solvent power means increase of urate in the blood, so long as there is urate anywhere in the body to be dissolved; and by influencing the solvent power of the blood we can influence within limits the amount of uric acid it contains; we can also influence it indirectly by the amount of uric acid we introduce ready formed in the food.

Second, excess of uric acid in the blood means contemporaneous excess of uric acid over urea in the urine: though as the urine in the bladder may be a mixture of urines excreted under several different conditions of blood, it must not be expected that the amount in the two fluids will correspond too closely.

This rule probably holds in all cases in physiology, but in pathology there is at least one well-marked exception to it, namely, nephritis; for in this condition the alkalinity of the kidney is probably diminished by the irritative processes going on in it, so that there may be (and according to Professor v. Jaksch there is) excess of uric acid in the blood, and yet it may be unable to pass the kidney into the urine. Hence we get in nephritis chronic retention of urates and chronic uricacidæmia (of which the signs are well-marked) without excess of urates in the urine.

Third, the quantity of urate in the various organs and tissues seems to stand in a certain order of proportion: thus, the liver and spleen have most, the kidney decidedly less, and the muscles least; the quantity in the blood varies considerably, but it always contains less, often much less, than the liver or spleen from the same body.

The quantities found after death in the blood again bear fairly definite relations to certain diseases; in pneumonia cases there is almost sure to be a large quantity; but in meningitis and other cases in which the temperature is high, and rising at death, there will be very little; again, in death from chronic wasting disease there will be a good deal, especially if there are urate deposits in the joints.

In the case in which the kidney contained so-called uric acid

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infarcts the temperature was high, and rising at death, which was due to marasmus; we should, therefore, expect very little urate in the blood, because it had been driven out of it, and the infarcts in the kidney probably show us one of the places into which it had been driven, there being, in fact, a gout of the kidney, this possibly being secondary to the irritation of previous uricacidæmia.

It thus seems to me to be practically certain that when uric acid is found in excess in the blood after death, it was in excess in that fluid at the time of death, and was passing from it in excess in the urine; and the excess in both fluids is due to the action of the same causes which determine excess in them during life.

I have shown that I can alter the amount of uric acid in the urine at any time, and that in addition to the above argument I have good clinical reasons for believing that I alter at the same time the amount in the blood.

That when I increase the amount in the blood by giving an alkali, I at once bring about obstruction of the capillaries throughout the body, thus raising the blood pressure and slowing the heart, and causing deficient circulation in numerous organs, the effect of which is soon visible in cold surface and extremities, mental depression or headache, and scanty urine containing a relative excess of uric acid.

If I now reverse the process by giving an acid I at once free all the capillaries, and the uric acid is driven out of the blood into the liver, spleen, joints, &c., and if much of it is sent into the latter it generally renders its presence clinically evident by a certain amount of shooting and pricking pain, or more severe irritation up to distinct arthritis; the free capillaries allow a lowering of the blood pressure and the heart quickens its pace, the surface and extremities become warm, the mind is clear and tranquil, the urine increases in quantity and shows diminished uric acid.

That the alterations in the amount of uric acid in the urine so produced are alterations of excretion merely, and that the quantity to be found in the blood at any time depends on its solvent power for uric acid, the amount daily introduced in the food, and the amount previously stored in the liver, spleen, joints, and other tissues on which the solvent can act. That when the alkalinity of the blood (*i.e.*, its solvent power for uric acid) is reduced it contains little or none; but when its alkalinity is increased it may contain a very large quantity.

That, as I have previously pointed out, all fluctuations in excretion taken over a long period of time practically balance each

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other, giving a result near what I believe to represent the real formation of uric acid, viz., 1 of uric acid to 35 or 40 of urea.

That though the large excretion of uric acid in splenic leucocythæmia, for instance, looks for a time like excessive formation, it is probably merely the passage out of the body of large amounts of uric acid which were retained in the early febrile stages of the disease. Thus, in a case of this kind I was able to examine after death, I found in the blood ·06 per cent., a very large liver and spleen contained between them 100 grains of it, there were urate calculi in one kidney and erosion in the great toe joint, but no deposit of urates there (see "St. Bartholomew's Hospital *Post-mortem* Book," case of N. T., age 32, April 25, 1892). Here the urates were being dissolved and passed out, and some of them unfortunately got deposited in the kidney on the way, and probably the liver and spleen contained much more uric acid earlier in the disease, for in these cases we know that there are often intercurrent pyrexial attacks during which the spleen enlarges (see *Lancet*, vol. i., 1892, p. 965), and during which I would add, the store of urates in the liver, spleen, and joints, and the body generally is increased. So that while I do not deny that a process of which I have no knowledge, viz., excessive formation of uric acid, may nevertheless occur (in excess that is of the usual relation to urea) I am in a position to assert that I believe all my results, as well as those of Professor v. Jaksch, can be explained by fluctuations in excretion, aided, as is generally the case, by more or less constant introduction, and further, that all the results which can be produced by drugs are in favour of this explanation, but are quite inexplicable on any theory of excessive formation or deficient oxidation.

If, for instance, the plus excretion of uric acid under alkalies or salicylates (figs. 6 and 8) is due to a plus formation, why does it, except under pathological conditions, not continue for more than two or three days? And even in pathological conditions it does not continue long, for in the case of splenic leucocythæmia, of which I give notes in chapter xii., a course of salicylate of soda sensibly diminished the excretion; while at the first administration of the drug I got excretions of 1 of uric acid for 12 of urea, it gradually diminished as the drug was continued down to 1 to 24 or less; in other words the stores of urate in the body were slowly being reduced.

The facts above pointed out, that the liver, spleen, and joints contain large amounts of uric acid, are in accord with Sir A. Garrod's theory, and with my explanation of my results; and in accordance with these the amounts in all these organs and tissues can be increased or diminished at pleasure.

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That this explanation satisfactorily accounts on the one hand for the well-known physiological fluctuations in the excretion of uric acid, and on the other for the previously recorded relations of a whole series of diseases, as, for instance, the alternation of gouty arthritis (*i.e.*, retention of uric acid going on in the joints and its absence from the blood), with such diseases as headache, epilepsy, mental depression, and glycosuria, with excess of uric acid in the blood and urine. The arthritis corresponding with free capillaries and low tension pulse from absence of uric acid from the blood, and the latter diseases with obstructed capillaries and high tension pulse from the excess of uric acid in the blood.

That in all these cases the excretion of uric acid in the urine corresponds with the amount in the blood, and that the facts about these diseases have been recorded by others who had no knowledge of their real relation to uric acid.

It seems to me that it is impossible to explain these facts either on the theory of excessive formation or on that of deficient oxidation, while Sir A. Garrod's dictum in the case of lead, "the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion," serves with the help of our more recent knowledge about introduction, to explain the whole situation.

It is now, I hope, obvious that we can not only explain all the physiological fluctuations in the excretion of urates and most of the pathological alterations as well; but that in accordance with my law of solubilities we can imitate nature and demonstrate the effects of uricacidæmia on the function, nutrition, and structure of the tissues of the human body to any required extent; and where the urates already in the body are insufficient for our purpose, we can increase them by the simple process of taking them in one form or another, by the mouth (see also chapter xii.).

It is, I know, believed by some of my fellow workers that Horbaczewski has demonstrated that uric acid is formed from the nuclein of cells, especially that of white blood cells.

And supposing for a moment that we take this as a proved fact, I will merely point out that it affects in no way either the facts I am now bringing forward, or the conclusions I found upon them.

For if it be true that the nuclein of certain cells is converted into uric acid, the rest of the cell may be similarly converted into urea, and the relative formation of these two substances may not be one bit affected thereby. This would be quite on all fours with the suggestion of Sir A. Garrod previously referred to, that certain cells in the kidney form urea, and certain other cells less in number form uric acid.

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Horbaczewski's observation that feeding on nuclein increases the excretion of uric acid is probably quite correct, but to my mind this by no means amounts to proof that there is any new formation of uric acid; for in the first place is it quite certain that the nuclein or the spleen pulp from which it is obtained does not contain xanthin, hypoxanthin, &c., which is merely introduced into the body as the previous figures show that it can be, and in the second place, is it not a fact that spleen pulp and nuclein contain phosphates and that these phosphates may increase the excretion of uric acid by acting as solvents (see fig. 7)? If this is the case, the administration of nuclein after a course of salicylates would produce less increase in the excretion of uric acid than the same quantity of nuclein administered before it.

But as I have said, Horbaczewski's conclusions affect me but little; if they prove to be true we shall merely have to add nuclein on to the list of substances above given, which are either uric acid or so closely related to it that human physiology makes short work of the small difference between them.

It really matters nothing to me whether uric acid is present in animal tissues as nuclein, as xanthin, hypoxanthin, or as urates visible to the naked eye, I am only concerned with the fact that when taken as food they produce disease by introducing this uric acid into the body of man; and this is the answer to the question which originated my research.

If it was true that uric acid when swallowed was at once converted into urea, as used to be supposed, then Horbaczewski's conclusions would stand on much stronger ground, for any increase of uric acid, he observes, must be due to new formation; but my results show that uric acid in foods is not converted into urea, on the contrary, it is absorbed unchanged into the blood, and passes gradually into the urine in quantity directly proportional to the amount introduced.

My researches then return me this answer to my question as to the connection between the ingestion of animal tissues and their products and uric acid in other forms, and the causation of the uric acid headache (migraine), that these substances not only introduce a considerable quantity of uric acid into the body, but this uric acid, in process of introduction, interferes with the solubility in the blood of uric acid previously formed in, or introduced into, the body; and in both these ways tends to form a store of uric acid in certain organs and tissues of the body.

As the result of more or less natural changes in the alkalinity of

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the blood, the urates thus stored up tend from time to time to pass into solution, and uric acid may then for a time be present in the blood in considerable excess, and this excess of uric acid produces such changes in the circulation as are amply sufficient to account for the pain in the head.

Lastly, they show that this headache can be completely prevented by stopping this needless introduction of uric acid, and that this can be done without reducing urea below the physiological level of 3½ grs. per lb. per day, if care is taken to get the required nitrogen from substances which contain little or no uric acid or xanthin compounds. So that we should probably not be very far wrong as regards this country if we put down the uric acid headache and most of its concomitant symptoms to poisoning by the flesh of animals, more or less aided by theïne and similar vegetable alkaloids, and "the uric acid diathesis," to which these troubles were said to be due, is thus seen to be nothing but a myth.[1]

If this was the only result of my research I should have no reason to be sorry that my sufferings induced me to undertake it, but in the course of this research it has gradually become evident that an enormous number of the diseases of the human body own a causation which is practically identical with that of the uric acid headache, and further, that uric acid, in controlling the circulation, exercises a directing power over the physiology of the human body to an extent which was quite undreamed of at the beginning of this research.

In the chapters which follow I hope we shall see that the knowledge thus obtained has the best hall mark of truth, in that it gives us a remarkable increase of power both to prevent and cure disease.

[1] See article on "'The Uric Acid Diathesis,' are we to continue to believe in it?"—*Edinburgh Medical Journal*, July, 1897.

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CHAPTER IV.

Uric Acid and Metabolism.

At this point I propose, in order to give my readers a grasp of the subject, which may be of some practical utility, to state in a few words what we have already learned, and in equally few words what we seem likely to learn in the chapters that follow; leaving them to judge when they have read these chapters whether my statements are sufficiently supported. And I would before doing so remind them again that I am presenting to them no finished picture, but a preliminary communication on a progressive research, on a subject which is still plastic in all directions, and with regard to which much still remains to be learned.

We see then as the result of the researches mentioned in previous chapters, that the uric acid daily excreted in the urine comes, or may come, from three sources: (1) the uric acid or urate formed out of nitrogenous substances along with a certain amount of urea, probably in the proportion of 1 of uric acid to 35 or 40 of urea. (2) Uric acid, urates, or other members of the xanthin group, as caffeine and other vegetable alkaloids introduced with the food. (3) Uric acid or urates previously stored in the body which pass into the blood whenever the alkalinity of that fluid favours their solution in it.

I may here state that uric acid in the title of this book and generally throughout the book itself, unless otherwise specified, is used as an inclusive term, comprehending uric acid and its salts.

When in the 24 hours urine uric acid is present in the relation to urea of 1 to 35, we conclude that this uric acid was formed along with the urea of that day, and passed directly down the ureter into the urine, and that there was no uric acid furnished direct from the food or from the stores in the body. If any uric acid was introduced in the food this was not allowed to remain in the blood, because the conditions of that fluid were unfavourable to its solubility, and for the same reason no uric acid was taken up from the stores in the body.

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If, however, uric acid was excreted in the relation of 1—20 or 25 of urea, we conclude that the excess over formation (1—35) is made up from uric acid introduced with the food or taken up from the deposits in the body, or both.

Under these conditions it is quite easy to understand why all substances which form soluble compounds with uric acid, or increase its solubility in the blood, should increase its excretion; and why all substances which form insoluble compounds with it, or diminish its solubility in the blood, should diminish its excretion.

If, on the other hand, the excretion of uric acid is very low, having the relation to urea of 1—45 or 1—50, we must conclude that some of the uric acid formed on this day met with conditions in the kidney which were unfavourable to its solubility, and was retained there instead of passing at once down the ureter, and we know that the kidneys may contain an amount which varies from a small percentage up to a quantity which is plainly visible to the eye (see p. 73.)

I thus regard the formation of uric acid in the body as practically constant in relation to urea; while excretion varies partly with the conditions affecting its solubility in the blood and partly with the quantities introduced in the food, or previously retained in the body, *i.e.*, the quantities available for solution.,

I absolutely disbelieve in the formation of uric acid as a cause of disease; nor do I see any proof that the gouty man forms any more than the non-gouty in relation to his urea; but the gouty man often indulges largely in animal food, and as a result, forms more urea per pound of body weight than the physiologists would allow him, and uric acid in proportion; and he also absorbs directly from his food a considerable quantity of uric acid or xanthin compounds. I take, therefore, a hopeful view in regard to these diseases, because these errors of diet can be eliminated: but if there really was an excessive formation of uric acid, this might be beyond our control.

It is obviously then in our power to control the excretion of uric acid by controlling the conditions affecting its solubility, and also the quantities directly introduced in the food, or formed from it.

From the clinical history of the uric acid headache we learn that at the time of the attack, when there is an excess of uric acid in the blood and in the urine, the pulse is generally slow, and of high tension.

And it will appear in the next chapter that this is due to obstruction of the capillaries, of which there is abundant evidence in the cold skin and extremities that accompany the headache. And

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a very little experimentation will, I believe, suffice to convince any one that obstruction of the capillaries varies directly with the uric acid that is circulating in the blood, even if fig. 5 does not of itself suffice to prove it. And this obstruction of capillaries will produce two results: (1) a rise of blood pressure in the heart and great vessels on the proximal side of the obstructed vessels—high arterial tension, or high blood pressure, and (2) a deficient circulation and interchange between the blood and the tissues in, and on the distal side of, the obstructed vessels.

It follows from this that all drugs and disease processes which diminish the excretion of uric acid and clear it out of the blood, will lower blood pressure and improve the circulation through all the organs and tissues of the body.

Drugs have already been mentioned, and the most important disease process which has this effect is fever, which diminishes the alkalinity of the blood, and thus prevents its holding much urate in solution.

Conversely, drugs and disease processes which increase the excretion of uric acid and bring it through the blood in increased quantity will raise blood pressure, and diminish or hinder the circulation through all the organs and tissues of the body.

The most important disease processes which produce this effect are Bright's disease, post-febrile conditions, dyspepsia, splenic leucocythæmia, marasmus, and the cachexia of new growths, &c., for in all these conditions of low or failing nutrition there is commonly some increase of the alkalinity of the blood rendering it a more than usually good solvent of uric acid; and in post-febrile conditions not only does the blood thus become a good solvent of uric acid, but a large supply of uric acid is present ready to be dissolved, namely, that which was held back and retained during the low alkalinity of the acute febrile period.

Now, other things being equal, a freeing of the capillaries of the kidneys means a free flow of urinary water, and their obstruction means scanty water; for this reason the urine is scanty (30 cc. per hour) during the uric acid headache (migraine) and profuse (60—160 cc. per hour), during the minus excretion of urates which precedes and follows it.

And not only is this true in pathology, but so constant is the relation of obstructed capillaries to uric acid, that in physiology also, in every one from hour to hour and day to day the urinary water varies inversely as the uric acid excreted along with it; or to state it as accurately as possible, other things being equal, the more

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the excretion of uric acid exceeds the relation to urea of 1 to 35 the more scanty will be the corresponding hourly or daily excretion of water, and *vice versâ*, because as we have seen from previous arguments the uric acid which is excreted in excess of formation (1—35) probably passes through the blood on its way to the kidneys.

It follows from this that all drugs and disease processes which diminish the excretion of uric acid and clear it out of the blood must increase the flow of urinary water, and this I believe represents in its simplest terms the *modus operandi* of the great majority of so-called diuretic drugs.

And drugs and disease processes which produce or are accompanied by an increased excretion of uric acid will also be accompanied by a scanty excretion of urinary water; so that the hourly excretion of urinary water being known, the greater or less excretion of uric acid can be calculated from it with sufficient accuracy for many clinical purposes.

This relation between uric acid and water can be seen in nearly every figure in this book, and during the years I have been estimating my own excreta I have not met with anything that could really be called an exception to the rule, if one bears in mind that the excretion of water is dependent partly on the freedom or obstruction of capillaries and partly on the supply of water available for excretion, for obviously no amount of freedom of capillaries will bring about a diuresis when all fluids have been drained from the blood and tissues by vomiting, diarrhœa or perspiration; but conversely slight and imperfect freeing of capillaries may produce a marked diuresis when there is an excess of water in the blood and tissues (dropsy).

One to 33 is the old relation of uric acid to urea in excretion, which I arrived at after a few months' work, and it forms the basis of all the older curves of excretion in the book. Further investigation now seems to show that while the relative formation of uric acid to urea is about 1—35, as in the more recent curves, excretion varies greatly from this with the amount of urate available for solution previously stored in the body, and with the amount daily introduced in the food.

With the exception of gout and rheumatism, all the diseases connected with uric acid are due to its effects on blood pressure and the interstitial circulation of organs and tissues throughout the body.

Thus headache, fits, mental depression, and bad temper, as also vertigo and a host of minor functional disturbances, represent the effects direct and indirect of high blood pressure on the intra-cranial circulation.

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In saying this, as in all I shall have to say, I wish it to be understood that while I consider uric acid to be a cause, often the most important cause of these disturbances, I should never go so far as to put it down as the only cause; and in the chapters which treat of the cerebral circulation, it will, I hope, be quite evident that other causes may produce similar alterations in the cerebral circulation, and, therefore, similar symptoms.

The well-known symptoms of high blood pressure represent the effects of uric acid in obstructing the capillaries and raising the pressure in the arterial system behind them.

Asthma and chronic bronchitis again probably represent some of the effects of high blood pressure and obstructed capillaries on the bronchial and pulmonary circulation, and this probably explains the relation so often seen between these diseases on the one hand, and gout and chronic Bright's disease on the other.

Dyspepsia may undoubtedly be produced by obstructed capillaries in the stomach and intestines, which inhibit gastro-intestinal digestion and allow putrefactive processes to take their place; and this again will explain at least part of the relationship between dyspepsia and such troubles as headache, epilepsy, and mental depression, or between dyspepsia and Raynaud's disease, or paroxysmal hæmoglobinuria, or anæmia.

In the liver again, just as in the stomach or intestines, we may obviously get more or less stasis or congestion as a direct or indirect result of the circulatory changes produced by uric acid.

Precisely the same thing applies word for word to the kidney, and here we have a very obvious and tangible result of the changes so produced in its circulation, in the fluctuations in the urinary water previously referred to.

Now, any excess of water in the blood and tissue fluids is promptly excreted so long as the circulation through the renal arterioles and capillaries is free.

But the circulation through the renal capillaries, which we must remember are doubled or reduplicated, may fail for two reasons: (1) that the capillaries are obstructed so that a normal heart cannot drive blood through them (as in uricacidæmia), or (2) that the capillaries are normally free, but the heart is weak (strain, debility, morbus cordis) and is unable to drive blood through them.

In either case there is retention of fluids in the blood and tissues, and in both cases the heart is not up to its work either absolutely or relatively.

In (1) we must treat the uricacidæmia, in (2) the heart, taking

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care at the same time that there is no uricacidæmia, for practically (1) and (2) often act together.

The same thing is seen in the salivary and probably in all other glands; and, in accordance with this, when a uric acid headache is present and the urinary water is scanty, the mouth also tends to be dry or sticky, and the saliva is scanty; and when the headache has been cured by acids, opium, mercury, iodides, or any of the drugs which clear uric acid out of the blood—not only is there a diuresis, but the saliva also becomes relatively profuse.

And we shall see also in chapter ix. that exactly the same thing applies to the excretion of water from the lungs, which rises and falls with the urinary water and other secretions, and inversely with the uric acid.

In the muscles also there can be little doubt that uricacidæmia produces deficient circulation and deficient removal of waste products, though probably the disinclination for muscular exertion, which is so marked a feature in attacks of migraine or mental depression, is due partly to the condition of the nerve centres; still, I think that cramps and other slight disturbances of muscle function are not improbably sometimes due to the deficient circulation of uricacidæmia (see also the Causation of Fatigue in chapter viii.).

The skin also has its circulation and nutrition very markedly influenced by uric acid, both in physiology (fig. 5) and in pathology, as witness the very pale and cold surface commonly seen in attacks of migraine, and in conditions in which there is is for some time a continual excess of uric acid in the blood, as in post-febrile conditions, marasmus, and chronic dyspepsia, the nutrition of the skin may be interfered with to an extent which may account for not a few eruptions, especially ulcerative eruptions, slow healing of wounds and other troubles; and in these conditions I am in the habit of ordering drugs that clear the blood of uric acid, in full confidence that if there is no organic disease I shall be able to improve the nutrition of the skin and facilitate the healing of wounds and the clearing up of rashes. Such a consideration explains the frequent time connection between skin eruptions and menstruation in women, for menstruation is nearly always accompanied by a certain amount of dyspepsia and lowered nutrition, and the uricacidæmia which results from it (see chapter xii.).

But the effect of menstruation on the excretion of uric acid has a much wider bearing on the causation of disease than the production of a few skin eruptions would imply, and I will now therefore give a figure to illustrate the fluctuations it may produce.

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Fig. 30 shows the effect on the excretions of normal menstruation in a woman aged 36 in ordinary health.

On November 13, the first day of menstruation, uric acid is fairly close to urea, and urinary water is fairly high.

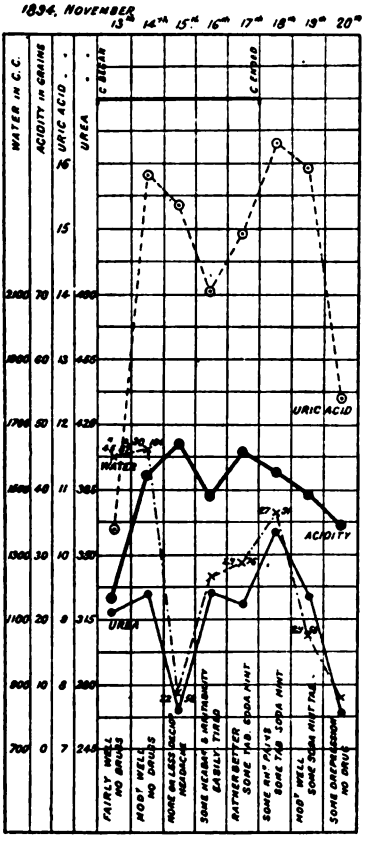

FIG. 30.—EXCRETION OF URIC ACID DURING MENSTRUATION.

On the two following days uric acid rises and remains very high, and on the second of these days urea and water fall very decidedly. Acidity follows the uric acid much more closely than the urea, and its rise is probably much more the result of the excess of uric acid in the urine than of any change in the alkalinity of the blood, and

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indeed with the fall of urea on the 15th, the blood probably became more alkaline. On the 16th uric acid falls, but rises again on the 17th, which is the last day of the menstrual flux. On the 18th and 19th it rises still further, but falls very decidedly on the 20th.

Urea and water rise all the way from the 15th to the 18th, and then fall again sharply on the 19th and 20th, this fall being very probably in part due to the high uric acid on the 18th and 19th.

On the 15th, along with the high uric acid and falling urea, there was some decided headache, and on the 16th there was headache and increased irritability; on the 17th she felt rather better, but on the 18th there were some distinct rheumatic pains, and I think it is possible that the rise of urea and of water on this day was due to some slight febrile movement accompanying the rheumatic pains. On the 19th she felt fairly well, but was taking some soda mint tabloids for the relief of dyspepsia and other minor troubles, and on the 20th there was some depression due to the falling urea and the still rather high uric acid.

We see then so far as this figure goes that menstruation at its onset may be accompanied by a fairly normal excretion of uric acid, but this is quickly followed by a very marked rise in excretion which continues with some fluctuation right through it, and even lasts for 2 to 3 or more days after the flow has ceased.

That these rises of uric acid are accompanied by headache, irritability and depression, with some dyspepsia and very marked falls of urea; in a word by the usual signs of uricacidæmia and the impeded circulation and diminished metabolism which it produces.

Thanks to the kind help of my friend, Mr. A. G. Ewbank, formerly house physician to the Metropolitan Hospital, I was able to get the excretions in several other cases during menstruation, and though they vary somewhat, and in some cases are complicated by the presence of active disease, they all agree in showing that menstruation is generally accompanied by a plus excretion of uric acid, especially towards the end of, or after the period was over, and in cases where I got the excretion a few days before the period began, it rather appeared as if its onset was accompanied by a diminished excretion of uric acid and a period of stimulation. I was unfortunately unable to get this in fig. 30, but the uric acid was in fairly normal position on November 13, the first day of the period.

It thus appears probable that menstruation merely causes a fluctuation in the excretion of uric acid, a diminished excretion or retention just before or at the beginning of the period, followed by a

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corresponding plus excretion during the period and just after its termination.

These facts enable us to explain very completely the connection between menstruation on the one hand, and such troubles as headache, epilepsy, mental depression, dyspepsia, skin eruptions, rheumatism and catarrh on the other; in a word, we have here an epitome of the causation of disease by uric acid. Menstruation causes a fluctuation in the excretion of uric acid and in the amount passing through the blood, and the uric acid in the blood by controlling the circulation, dominates the function, nutrition and metabolism of the whole body.

So that just before and at the beginning of menstruation we have a diminished excretion or retention of uric acid, with which goes a free circulation, a rise of urea and acidity, and a general stimulation of function, nutrition and metabolism throughout the body, with this there goes increased activity of mind and body, and a sense of well being; neither headache, fits, depression, dyspepsia or catarrh come at this time, but rheumatism if present may be slightly increased.

On this there follows an excessive excretion of uric acid, with the passage of its excess through the blood, and as a result the circulation is everywhere hindered and obstructed, nutrition and metabolism diminish, and there is a more or less marked fall of urea; in a word uricacidæmia and its results. With this there comes increasing headache, irritability and mental depression, with fits if the patient is subject to them; dyspepsia begins or is increased, and skin eruptions appear or are distinctly aggravated, or if anyone in the house has a cold, she is liable to take it just at this time; on the other hand, rheumatism, if previously present, is often distinctly better, because rheumatism is always better with a plus excretion of uric acid; hence the alternation between rheumatism and migraine which has been observed in so many cases; what cures the one aggravates the other.

It is interesting in this connection to remember that Dr. Oliver has noted, by means of the arteriometer, the high blood pressure of menstruation and the absence of postural variation in this physiological condition, which resembles the similar absence of postural variation met with in the gouty and in migraine (see *British Medical Journal*, 1896, vol. i., p. 1375).

In the case of fig. 30, after the first onset of uricacidæmia and depression there follows a rise of urea and acidity from November 15 to 18, and with this the headache and dyspepsia get better, but some rheumatic pains become prominent.

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Later on the uricacidæmia again causes diminished metabolism, and the rheumatic pains again give place to dyspepsia and mental depression.

And there is still one more physiological connection of menstruation which may I think be eventually found to explain a corresponding pathological section.

I refer to the well-known fact that the menstrual period in many women is accompanied by enlargement of the thyroid gland.

Here then we have three things together which are perhaps of some importance, a fluctuation in the excretion of uric acid with its temporary excess in the urine and the blood; as the result of this a temporary period of high blood pressure, and with this, possibly in connection with it, enlargement of the thyroid.

Have we here a side light on the causation of Graves' disease and its frequent occurrence in women, for the chief signs of this disease are but exaggerations of those which occur in physiology, and the quick action of the heart may be but the ordinary effect of high blood pressure when the heart fails before it; in a word Graves' disease may be a result of high blood pressure originating in the recurrent high blood pressure and uricacidæmia of each menstrual period.

And while considering this subject we must not lose sight of the fact that at least one drug (the chloride of calcium), which has obtained some reputation for curing or relieving Graves' disease, has as I have pointed out a very distinct and decided effect in lowering blood pressure, which it does by clearing the blood of uric acid.

A case or two I have seen recently brought this again into my mind, and made me decide to give the treatment of Graves' disease a thorough trial from this point of view.

The most interesting of these cases was that of a young man, aged 22, sent to me by Dr. Maclaren, of Harley Street, and his history showed that a few years ago, after much sedentary work and rather excessive smoking, he suddenly took a good deal of violent exertion, and then began to suffer from attacks of palpitation and threatenings of syncope.

He was carefully treated for heart weakness or strain, and after a course of Schott treatment the condition of the heart improved, and he then began to suffer from severe headaches, apparently ordinary migraine (uric acid headache), from which he had suffered periodically for some years, since puberty.

This continued for some time, and he was able to go back to his professional work again, and then again after hard work and

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exposure his heart got weak, and he got the palpitation attacks again and the headaches went off.

Again he was treated with the Schott method and very numerous tonics, and was also fed up on raw beef juice, beef jelly, and a great excess of nitrogenous food.

The condition of the heart again improved, and again the headaches returned, having been absent while it was weak.

When I saw him a little after this I found the following conditions:—

Is decidedly pale, but fairly nourished. Eyes slightly prominent, and there is distinct fulness of the lower part of the neck, over the thyroid region. Patient volunteered the statement that he now had to wear collars ½-inch larger than a year ago.

Pulse rate 96. Apex beat slightly outside the left nipple line. First sound reduplicated over the septum of the ventricles, and second sound loud both at apex and base.

At present he is fairly well, and only had one slight headache about a week ago, which was cured by tea.

Such is a short outline of what I think is the most interesting medical case I have ever seen; for it is interesting not only for what it tells us certainly, but in what it merely suggests.

I think it may be read as follows in summary, cardiac strain from exertion following much sedentary work, and the muscular depressant action of excess of tobacco.

Relief of cardiac condition and return of the old headaches, due to high blood pressure.

Relapse of the heart and disappearance of the headaches.

Relief of the cardiac condition, and excess of nitrogenous food taken.

Present condition, some little failure and dilatation of the heart, headaches comparatively slight, pulse quick. And with these signs there is slight prominence of the eyeballs and distinct enlargement of the neck (? early Graves' disease).

This case leaves in my mind no doubt that he suffered all along from high blood pressure, as shown by the old migraine. That after the strain the heart first failed and then recovered under treatment, only to fail again and again recover, because the cause of the high blood pressure was never removed; hence the headaches due to the high blood pressure came and went with the ability of the heart to keep up the blood pressure or its failure before it.

The condition when seen by me was one more or less half way between severe cardiac failure on the one hand, and high blood

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pressure with severe headaches on the other; the pulse was quick, there was some dilatation of the heart and the headaches were comparatively slight in accordance with this; and there were now associated with these what might be the signs of early Graves' disease.

But be this as it may there is no room for doubt in my mind that if the blood pressure had been treated and reduced by putting him on a uric acid free diet from the time of his first cardiac strain, he would have recovered both more quickly and more permanently, and would not have had the alternating signs of heart failure on the one hand or headache on the other, and might in all probability have also escaped the more threatening signs of Graves' disease.

It is now difficult to say what may be the result and how far quickened heart's action, dilated heart, enlarged thyroid, and prominent eyeballs, point to organic and incurable disease. The case is incomplete, but I give it here for its great interest and suggestiveness, and because it gives an absolutely convincing demonstration of the pathology of the uric acid headache, which may be taken along with what I shall have to say of the action of antipyrin in this headache in chapter vi.

With regard to prognosis, I may mention that before I saw the above case, the idea that Graves' disease might be a result of high blood pressure, occurring most frequently in women, because of their monthly fluctuation in blood pressure had led me to put an hospital patient of mine on to a uric acid free diet, and that this even in a few weeks apparently gave some relief, as her pulse rate fell from 120 to 92, and her face became less congested. This case had been under observation for several years, had been given all the drugs supposed to be useful in the condition, though ice to the thyroid seemed to do more than anything else, and she had had the right lobe of the thyroid removed by my colleague, Mr. W. H. A. Jacobson, with the apparent result of lessening the prominence of the right eyeball. Still, in spite of all treatment up to the time of altering diet she had all the signs of progressive dilatation of the heart.

In marked contrast with these effects of menstruation note the effects of normal pregnancy. Here we have a steady upward progression of nutrition and metabolism; urea and acidity rise steadily, and the blood is consequently cleared and kept clear of uric acid.

For this reason in normal pregnancy, headache, fits, mental depression, dyspepsia, asthma, and other diseases, such as psoriasis;

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in a word, all diseases due to an excess of uric acid in the blood are remarkable by their absence, while Sir A. Garrod (prev. ref. p. 212) tells us, just as we should expect, that women occasionally suffer from gout during pregnancy, and not only so, but there is a common idea among the people which is mentioned by Sir W. F. Wade (*British Medical Journal*, 1872, vol. ii.) and which I believe to be well founded, that pregnant women do not readily take diseases, such as colds, fevers, &c., to which they may be exposed. We shall see further on, that opium by giving its *habitués* freedom from uricacidæmia gives them also similar relative immunity from disease, and that bracing mountain climates also do the same to a certain extent. Normal pregnancy, therefore, corresponds to the first or stimulation stage of menstruation, and the diseases of the one to the diseases of the other. But if pregnancy is not normal, or if metabolism is upset by such a disturbance as vomiting, the picture is completely reversed; there is no rise of urea and acidity, on the contrary they fall, and the blood instead of being kept clear of uric acid is flooded with it, and the diseases which are due to this—headache, fits, depression, dyspepsia, asthma—in place of being diminished are present or increased, and the patient, instead of being proof against colds and fevers, is liable to take them; and indeed, if the upset of metabolism is at all severe, that last and worst stage of defective combustion, Bright's disease itself, may appear on the scene.

And in chapter xiii. we shall see a case in which such disturbance of pregnancy, perhaps aided by the altered pressure relations in the abdomen and some failure of the heart, did apparently bring on this disease.

With regard to infection, the point may be expressed shortly thus; in normal conditions, and still more in conditions of stimulated nutrition, when the blood is free from uric acid and the circulation is, in consequence, free and perfect in all the tissues, when digestion is perfect and metabolism complete; when, in a word, the fires of life burn strong and bright, the microbes of disease are burnt up and destroyed, and have no chance of taking root anywhere.

On the other hand, when under the reverse conditions, the draught is bad, combustion is incomplete and the fires run low, the microbes get a firm hold, and are able to multiply and produce the disease.

From this point of view the causation of fever is of extreme interest, for fever is accompanied by a general increase of combustion

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and metabolism, and, indeed, it looks very much as if it was a protective effort on the part of nature to stimulate the fires of life and burn out the invader, and it is interesting to note that Loewy and Richter (*Berl. Klin. Woch.*, March 1, 1897) found that artificially produced fever protected animals to some extent against microbic inoculation.

I shall have more to say on these points in treating of the causation of catarrh in chapter ix., and, indeed, I am here merely giving an outline of the part played by uric acid in the causation of disease, and each individual disease will be treated of separately in the chapters which follow.

To put these points in a nutshell, we may say that the effect of excess of uric acid in the blood is deficient and incomplete combustion, while the result of keeping the blood clear of it, no matter by which of the numerous means at our disposal this is accomplished, is satisfactory and complete combustion.

Previous writers have very often told us, and some are saying so still, that the excess of uric acid found in the urine in these conditions is the *result* of deficient combustion; my researches, however, show, and indeed, make the demonstration almost absolute, that the truth is the exact reverse of this, and that uric acid is the *cause* of the deficient combustion.

When pregnancy comes to an end, however, especially if labour is tedious and fatigue is great (see Fatigue, chapter viii.), the fires of life run low, and then the wet blanket in the shape of the uric acid stored during pregnancy, gets on top of them and keeps them down, and lactation may further add to the depression.

Under these conditions all or any of the diseases which were remarkable by their absence during normal pregnancy return in an aggravated form.

Before I leave fig. 30, I will just point out that it serves to explain certain observations made by others as to the effects of menstruation on metabolism; thus, in an article on "Stoffwechsel Während der Menstruation," by T. Schrader (in von Noorden's *Beitrage zur Lehre vom Stoffwechsel*, 1894, Heft. ii., S. 132), it is pointed out that menstruation is accompanied by a constant fall in the output of nitrogen by the fæces and urine, which is not the result of any alteration in diet, as this was purposely kept constant, but which Schrader thinks is due to a diminished formation of urea.

He proceeds to give an explanation which seems to be lacking in completeness, and for which I must refer my readers to the original article, but I think this diminished production of urea is sufficiently evident in fig. 30, and its causation by the deficient

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combustion and metabolism which excess of uric acid in the blood always produces is sufficiently clear.

It is, I believe, a universal law dominating both physiology and pathology, that high uric acid means low and falling urea, and low uric acid means rising and high urea, and this law, as we shall see, lies at the very root of such conditions as fatigue in physiology, and of many blood changes up to Bright's disease itself in pathology.

Lastly, I will just point out that the stimulation which accompanies the sexual act in men has an almost identical effect on nutrition and the excretion of uric acid, with that of menstruation in women.

The sexual act is no doubt a powerful stimulus to circulation, and is accompanied by muscular activity, but this is not pushed to the fatigue point, and consequently it produces a rise of urea and acidity, which, as we shall see in chapter viii., is the first effect of all exercise, and continues till the acidity is brought down by perspiration.

This rise of urea and acidity clears the blood of uric acid and produces a stimulation of nutrition and metabolism just as occurs apparently at the beginning of menstruation, but just as in menstruation and in the action of a long list of drugs, this primary retention of uric acid, the result of the stimulation is followed by a secondary plus excretion of uric acid or a rebound; and during this stage of the fluctuation, a man will suffer from similar troubles to those which affect women during or at the end of menstruation, and this is the reason that many men who suffer from the uric acid headache (migraine) have noticed that they often have an attack on the day following sexual intercourse (see chapter vi.)

It seems to me also to be a fact of some interest that the sexual appetite appears to increase with high and rising blood-pressure, and to be slight or in complete abeyance with low or falling blood-pressure, and as the sexual act itself tends, as above shown, to produce low and falling blood-pressure, it tends to remove the desire for repetition of the act.

Further, I think that as the sexual act produces low and falling blood-pressure, it will of necessity relieve conditions which are due to high and rising blood-pressure, such for instance as mental depression and bad temper; and unless my observation deceives me, we have here a connection between conditions of high blood-pressure with mental and bodily depression and the act of masturbation, for this act will relieve these conditions, and will tend to be practised for this purpose.

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I think, therefore, we should do well to bear this in mind in such cases, and where they are obviously associated with high blood-pressure, would do better to assist nature in lowering this pressure, rather than in attempting to fight against her with such feeble weapons as mental and moral suasion; that, in a word, we should treat the morbid conditions present in the circulation, and leave morality to right itself when a satisfactory cerebral circulation has been restored by the use of suitable diet or drugs.

I have been much interested to see that the connection between sexual appetite and blood-pressure, or what is the same thing, the mental conditions its changes produce, has been noticed by opium eaters in whom these changes of blood-pressure are seen to perfection, in whom also they are due, as elsewhere, to changes in the amount of uric acid present in the blood, and can be completely controlled by controlling the uric acid, as for instance, by means of salicylates (see fig. 15, and remarks on it).

Thus in "L'Encephale," 1887, p. 306, we are told by an opium *habitué* that during the stage of opium well-being, in which as we know the arterioles are relaxed and the blood-pressure low (see fig. 34 B), there is no desire for women, and that the difference of sexes ceases to exist; but that later on in the stage of rebound, misery, high blood-pressure (see fig. 34 A) and craving for a fresh dose of the drug, desire for women is great, and that contact brings calm with it, though the act can be repeated many times.

These effects of the sexual act on the blood-pressure account, no doubt, for the calm and good temper which follows the act, and also probably for the terrible storms of passion which may follow in either sex if the desire is not obtained, and when consequently the high-blood pressure is not relieved, and these in turn may account for not a few of the murders and suicides of every-day life (see chapter viii.) which are often so obviously connected with the sexual relations.

Here again my remarks about masturbation will apply, for the poor wretch under the dominion of uricacidæmia and high-blood pressure is in no way accountable for his or her acts, and is, as the jury truly put it, temporarily insane; and it is useless to appeal to the *mens insana* which is the result, while leaving untreated the *corpus insanum* which is the cause.

I would strongly recommend all those who are interested in the causation of disease by uric acid to read the interesting article just referred to, as it gives a most able summary of the evil effects of excess of this substance in the blood, as well as of the opposite

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effects of its more or less complete absence; it shows also quite clearly, I think, that the necessary increase of dose is due to the storing up of more and more uric acid, which is always ready to pass back into the blood the moment. the acidity is allowed to fall, and as opium diminishes appetite, and produces wasting as a result, more and more help from outside is continually required to keep the acidity from falling.

It demonstrates also that the action of opium in saving its *habitué* from diseases which others take, is the exact parallel of that of normal pregnancy and the exact reverse of the second stage of menstruation, and is due to its preventing uricacidæmia and keeping the fires of life at white heat.

That uricacidæmia affects the nutrition of the extremities as well as the skin, is seen in the pale, cold hands and feet which are so marked a symptom in migraine, in the "dead hand" of Bright's disease, and the still more marked alterations in nutrition met with in Raynaud's disease.

Last, but not least, an excess of uric acid seems to produce changes in the nutrition and structure of the blood itself, so that just as it is possible to cure anæmia by giving iron, it is also possible to produce anæmia by giving uric acid, and where the two are given together the uric acid overpowers the iron, and the blood either remains in *statu quo*, or deteriorates, and in my own person not only does my blood fraction—$\frac{\text{haemoglobin per cent.}}{\text{red cells per cent.}}$ vary in value from hour to hour and day to day with the quantity of uric acid passing through my blood, but it is possible to make it vary up or down at pleasure by giving uric acid or iron as required.

While speaking of the effects of uric acid on the blood, and while we have still not forgotten the effects of menstruation on uric acid as shown in fig. 30, I will pass on to fig. 31 which is a temperature chart of Mary H., aged 18, who was under my care in the Royal Hospital for Children and Women, suffering from chlorosis in October, 1894.

Up to October 12 her temperature was slightly raised, as is common in such cases and varied between 98·2 and 99·6. She was at first put on bismuth and Carlsbad salts for some dyspepsia, and on the 7th these were stopped, and she was put on pulv. ferri. carb., gr. x. three times a day. On the 13th the temperature became more irregular, with an evening rise and morning fall, and this continued on the 14th and 15th. On the 14th menstruation began and lasted three days till the evening of the 16th. On the 16th temperature was exactly normal both morning

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and evening. On the 17th it passed below normal, and remained there till the evening of the 21st, when it rose to 99·6, and on the following nights it did much the same, only falling below normal once on the morning of the 24th.

The pulse during the first thirteen days ranged from 72 to 102; during menstruation it was 108 on one day and 102 on another; during the subnormal temperature which followed on the 17th, 18th, 19th and 20th its highest rate was 96, and pulses of 66 were recorded on two mornings, and it once again fell to 66, with the subnormal temperature on the morning of the 24th.

I examined her blood on the 10th, 17th and 24th. On the 10th hæmoglobin was 35 per cent. and cells 120 per cent., $\frac{35}{120} = \cdot 29$. On the 17th hæmoglobin was 41 per cent., and cells 121 per cent. = ·33,

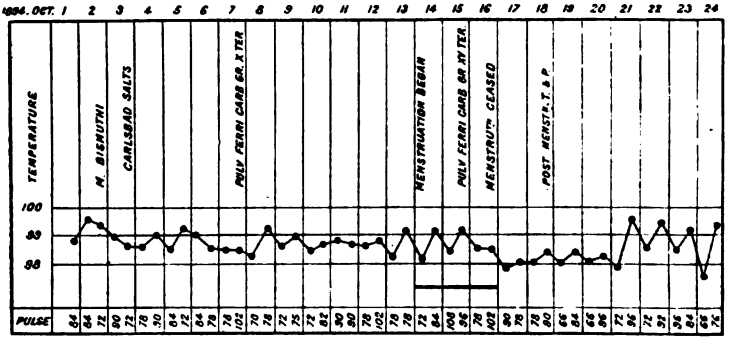

FIG. 31.—EFFECTS OF MENSTRUATION ON PULSE AND TEMPERATURE.

a rise of four places; and on the 24th hæmoglobin was 46 per cent. and cells 130 per cent. = ·35, a rise of only two places.

Now the object of this figure is to show the slight rises of temperature which precede and accompany the onset of menstruation, and the subnormal temperature and slow pulse which followed it, and to draw attention to the remarkable fact that while the blood decimal improved four places in the week, ending October 17th, it only improved two places in the week ending October 24th, in spite of the fact that the iron was continued the whole time, and was indeed increased to grs. xv., three times a day on the 15th.

I will now give what I believe to be the explanation of these facts: the rises of temperature on the 13th, 14th and 15th were due to the stimulation, with retention of uric acid, that preceded and accompanied the onset of menstruation, which produced, perhaps, a

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little rheumatism or other result of the storage of uric acid. On the 16th the temperature fell to normal, showing that the minus excretion of uric acid was giving way to a rebound and a plus excretion, and the subnormal temperature on the 17th, 18th, 19th, 20th and morning of the 21st showed that the plus excretion and the corresponding excess in the blood continued.

On the 21st the uric acid rebound came to an end, urea and acidity rose, and some of the remaining uric acid was driven out of the blood into the joints, causing the evening rises of temperature to the end of the figure, and such rheumatic pains would correspond with those of November 18, in fig. 30.

It seems probable, then, that Mary H. had a diminished excretion of uric acid just before and during the first two days of her menstruation, and that this was followed by a rebound or plus excretion on the last day of menstruation and four following days, and that these changes in the quantity of uric acid in the blood accounted for the fluctuations in temperature recorded in the figure, and for the facts that the pulse was at its quickest on the second day of menstruation, and at its slowest on the days of low temperature that followed it; for we know that the temperature is lowest in those hours of the day in which there is most uric acid in the blood, and highest in those hours of the evening in which there is least (fig. 5), also that the pulse is slowest in those hours of the day in which there is most uric acid in the blood, and quickest in those hours of the evening in which there is least.

Both pulse and temperature, therefore, point to there having been excess of uric acid in the blood from the 17th to the 21st, and the blood decimal apparently agrees in saying the same thing, for I have shown not only that my own blood decimal varies from hour to hour and day to day with the amount of uric acid that is passing through the blood, but that in chlorosis it is possible to make the blood decimal curve move up or down at pleasure by controlling the uric acid that passes through the blood (see figs. 46 to 49), and the fact that the blood decimal rose four points between the 10th and 17th, and only two points between the 17th and 24th, is evidence that there was some excess of uric acid passing through the blood between the two last-named dates.

I believe that menstruation will often be found to yield temperatures very similar to those in fig. 31, the low temperatures corresponding with the low urea, headache and depression, as on November 15 and 20 (fig. 30), and the high temperatures with the high urea and rheumatic pains on November 18.

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I notice also that Sir W. F. Wade makes the interesting remark that menstruation relieves the headache, depression and other signs of chlorosis for a time, but they return afterwards and are worse (*British Medical Journal*, 1872, vol. ii., p. 35). This, I have no doubt refers, as regards the improvement, to the early period of stimulation corresponding to the raised temperature, October 13, 14 and 15 (fig. 31) and the low uric acid November 13 (fig. 30), and as regards the subsequent deterioration to the subnormal temperature in fig. 31 and the high uric acid in fig. 30.

Sir W. F. Wade likens these effects of menstruation to those produced by venesection, and says that venesection gives similar relief; but that after each repetition the symptoms return more quickly and are more severe.

It is not difficult to see why a venesection should give relief, for every similar loss of blood is followed by a rise of temperature which is probably the result of the blood being cleared of uric acid by the venesection which will tend to reduce the alkalinity of the blood and so its power of holding uric acid in solution.

And this might raise the question whether the rise of temperature from the 13th to the 15th was not due to the loss of blood, but this figure itself shows us that the temperature was raised before the loss of blood began, and that it fell to normal on the 16th before the loss of blood had ceased.

When the excretion of uric acid exceeds the relation to the urea excreted along with it of 1—35 there is some excess of uric acid in the blood (uricacidæmia), and this excess is proportional to the extent by which uric acid exceeds this relation to urea, and proportional also to the absolute quantity of urea. Thus an excretion of 1—25 on a total urea excretion of 350 grs. a day will furnish 4·0 grs. of uric acid to pass through the blood on that day, while an excretion 1—25 in relation to an excretion of 600 grs. of urea will furnish 6·9 grs. of uric acid to pass through the blood. And it appears that the contraction of arterioles or obstruction of capillaries, and all the symptoms and phenomena which are secondary to this, are proportional to the absolute quantity of uric acid which is present in the blood from hour to hour.

If urea varies only with body weight, and does not go above the physiological level (3½ grs. per pound per day), then uric acid will vary only with body weight, and the amount available to pass through the blood will be relatively the same in all cases. But if a man takes far more animal food than is required to keep his urea at the physiological level, he will not only introduce more uric acid than

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the man who only takes just what is required, but he will also form more, just as he forms more urea than the other man, and will in both ways come to have a larger quantity available for solution in his blood. Here we see the evil effects of living almost entirely on animal food, as some people in these days have gradually accustomed themselves to do. On the other hand, urea can be kept quite well about the required physiological level if care is exercised not to take those foods which contain large quantities of uric acid or its equivalents: the normal formation of uric acid in relation to normal urea will do no harm if the unnecessary introduction of uric acid is kept as low as possible, and these two points—sufficient urea without unnecessary uric acid—must be the constant aim of diet treatment in these diseases.

In place of rheumatism and gout I see but one disease, an arthritic irritation due to the presence of urates, which under some circumstances will be limited to one joint (gout), or affect several joints contemporaneously or in succession and the heart also (rheumatism).

Ebstein and other experimenters have shown that the introduction of urates in solution into the tissues produces local irritation, and it rather appears that the irritation is greater when the urates are in solution, than when they are deposited in solid form. Indeed, we know that it is no very uncommon thing to find in the *post-mortem* room a toe joint plastered with urates when the patient had complained of no local irritation, and even given perhaps no history of gout. The urates had evidently been there some time, and had been causing no trouble. On the other hand the ingestion of a little acid wine or beer will cause, say often within half-an-hour, the retention of some urate (probably in solution) in certain joints, which from hard work or previous irritation are less alkaline than their fellows, and thus quickly bring about considerable pain and inflammation, which, whether it is called gout or rheumatism, is due to urate irritation. I have scores of times produced some such joint irritation in myself, knowing full well every step in the chain of causation; and having this knowledge, I have very many times been able to recognise the causation of joint irritation in gouty or rheumatic patients, by drugs given them by others, or myself, for other purposes.

Further, I will undertake to produce an arthritis, which shall be clinically indistinguishable from gout or rheumatism, in any member of the profession who is in good general health and will follow my instructions. All that is necessary to do is to get a little

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uric acid into the blood, and when one can see by the slow pulse, scanty urine, and more or less headache and mental depression, that it is actually present there, one must administer as quickly as possible some acid or other drug which interferes with the solubility of uric acid, and drives it out of the blood into the tissues (see cases in chapter xvi.). It will probably be also necessary to work or produce some slight irritation in, or in the neighbourhood of the joints we wish to be most affected; thus a man who gets gout because he drinks some extra pints of beer on Saturday night, gets it in the wrist of that hand which he has used most in his trade that evening, and we must imitate nature to this extent if we wish to produce the clinical picture of gout. But it is just the same with all the other diseases I have mentioned; each one of them can be produced or intensified by the intentional introduction of uric acid into the blood, bearing in mind the laws which govern its solubility in that fluid. So that if anyone is in doubt whether his headache is due to uric acid he has only to swallow certain quantities of the substance under conditions which do not interfere with its remaining in solution in the blood, and convince himself one way or the other. And the same method may be used for the investigation of many other diseases, and, as will be seen presently, I have myself applied it to investigate the causation of anæmia (chapter xii.).

In attempting to estimate the effects of uric acid on the metabolism of the body as a whole, it must never be forgotten that the depressant effect it produces tends to increase itself, so that once the ball is set rolling it will go on down the hill. Thus uric acid is commonly in excess in the blood, because that fluid is more than usually alkaline (*i.e.*, a more than usually good solvent of uric acid); but the effect of an excess of uric acid in the blood is a diminution of the capillary circulation in all the organs and tissues of the body, and as results of this we get, among other things, diminished digestion and absorption of food, and a diminished interchange between the blood and the tissues, that is, a general slackening of metabolism, and this in turn brings about a lessened formation of urea, and of acids and acid salts which usually keep pace with urea. But falling acidity of the urine means increasing alkalinity of the blood and, so long as plenty of urate is available for solution, more and more marked uricacidæmia, and thus depression of mind, body, and metabolism gets worse and worse, and there seems to be no end to it. But if, before the process has gone very far, and before depression of metabolism has led, as it ultimately does, to much atrophy of tissue, a drug is given, which clears the blood of uric

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acid, the process may be quickly and completely reversed, for the moment the blood is cleared of uric acid there is again a free circulation through all the organs and tissues; digestion and absorption of food are resumed, and free tissue metabolism goes on; up goes the formation of urea and of acids, a steady and progressive upward metabolism is started, and the blood is kept clear of uric acid.

I have often been asked by other observers whether the effects of small doses of drugs which clear the blood of uric acid are not out of all proportion to the quantity taken; why does a very minute dose of a nitrite, a few grains of a sulphate, or a small fraction of a grain of calomel, free the capillaries all over the body, cure headache or mental depression, and alter the whole condition of the sufferers? Truly the effect is out of all proportion to the dose, and much more uric acid may be retained than a fraction of a grain of calomel could possibly combine with.

But if we remember the facts just stated, that each of these drugs, if it is able to clear the blood of uric acid for only a minute or two, starts an upward metabolism which progresses long after the direct effect of the drug has come to an end, we shall have no difficulty in understanding the way in which these minute doses act.

The drug is like the percussion cap in the cartridge; it does not furnish the force which drives the bullet; it supplies, however, the spark which ignites the powder. Exactly the same explanation applies to the fact that an apparently insignificant dose of a drug will sometimes produce severe and long-lasting pains in the joints; here again the drug merely started a process which continues long after it has ceased to act.

It has been suggested by several of those who have done me the honour to review some of my writings on these subjects, that I have, to some extent, been led away by my personal interest and experiences to attach an undue importance to the rôle of uric acid in the production of disease; and the suggestion has found a ready echo in my own mind, for it has often appeared to me very probable that I might fall into this error.

In taking stock of my position, as I have done in this volume, and more especially in this chapter, I feel that while I am by no means free from the ordinary errors and sources of error that affect humanity, I can honestly say that I have spared no pains in the past and will spare none in the future to test in the most rigid manner possible all the assertions I have made; and that I made

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none at all until the evidence appeared to me to be very strong indeed.

For these reasons I have been truly delighted to find (as we have seen in the previous chapter) that uric acid taken by the mouth is at once absorbed and added on to the urates in the blood and tissues of the body; as this seems to place within our power the means of applying the experimental method to the causation of disease by uric acid.

I thus obtain not only a very convenient power of making more accurate experiments on myself; but anyone who doubts what I say with regard to the power of uric acid in producing changes in circulation, nutrition and metabolism, can very easily test most of the points in his own person.

I believe that it is now quite possible for any one who wishes to do so to raise his arterial tension, slow his pulse, and make his urine per hour scanty simply by swallowing uric acid. But he must bear in mind that the first effect of uric acid taken by the mouth is to raise the acidity of the urine and diminish the alkalinity of the blood, so that it drives uric acid out of the blood, and diminishes the excretion of that substance in the urine, and while it does this it lowers arterial tension, quickens the pulse, and increases the excretion of urine; so that a dose of uric acid, xanthin, hypoxanthin, or caffeine, will cure a uric acid headache. Next day, however, or as the acidity falls again, uric acid passes in excess into the blood, and the picture is reversed.

And I regard such an experiment made by man on his own body, as an infinitely better guide to the effects of uric acid on the arterioles and capillaries than an injection of any quantity of uric acid into the vessels of animals.

For even if I could inject, say, 10 grs. of uric acid into my own blood stream, we should get a freeing of capillaries and a fall of blood pressure rather than a rise; and further, unless my blood had been previously rendered strongly alkaline, this uric acid would not remain in it more than a very few moments at most; but would quickly be retained in the liver, spleen, joints, and other tissues, causing some gouty pains probably, but no rise of blood pressure.

To affect arterial tension with uric acid, you must first of all introduce it into the body, and then bring it through the blood in combination with an alkali.

On the other hand, as I have shown, the introduction of an alkali into the blood will produce no effect on arterial tension if there is no uric acid to combine with it; while mere absence of

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uric acid from the blood, owing to its previous removal by excretants, will allow of free capillaries, lowered tension, quick pulse, profuse urine, and improvement in value of the blood decimal (see also Fatigue, chapter viii.)

We may sum up this chapter then by saying that uric acid acts as a factor in the causation of disease in one of two ways—

(1) As a direct local irritant when it is present in any tissues in considerable quantity and probably still in solution or suspension as a colloid quadriurate (see next chapter.)

(2) As an obstructor of capillaries affecting on the one hand the circulation, nutrition, function and temperature of all the organs and tissues of the body, and on the other, producing high blood-pressure which directly affects the heart and the vessel walls, and otherwise influences the intra-cranial, thoracic and chylopoietic circulations.

It is chiefly as an obstructor of capillaries that we shall have to deal with uric acid in the following chapters.

We shall see that by this action on the circulation, it controls the physiology of every-day life, and determines the slow or quick combustion of the human body, just as shutting or opening the flues determines that of the kitchen fire.

We shall see that while the old theory that excess of uric acid in the urine was the result of deficient combustion explains nothing, our newly-acquired knowledge that excess of uric acid in the blood, of which the excess in the urine is the index, is the cause of the deficient combustion, explains everything.

We shall see that as a result of this knowledge, our power over physiology is doubled, and that over pathology trebled and quadrupled, and that in large fields of the treatment of disease, where empiricism reigned before, something approaching mathematical accuracy can now be substituted for it.

In a large number of disease processes it is absolutely true that when we have controlled the uric acid we have controlled the disease; and what we have to learn from the preceding chapters are the ways and means open to us for controlling uric acid; and in the chapters which follow the way in which uric acid acts in each disease, so that we may select the most suitable means for stopping its action, and where possible removing its results.

In every case we ought to be able to stop its action; but whether we shall be able to remove its results must depend on the nature of these results as well as on the kind of tissues affected. Thus, for instance, we ought to be able to dissolve out and remove urates from

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any tissue in the body: but the place they have occupied will then be filled by a scar and not by normal tissue; as I am accustomed to say, pouring water on the fire will not rebuild the ruins. So that while increase of knowledge greatly increases our power over disease, that power is very far indeed from being absolute.

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CHAPTER V.

Pulse Tension.

As previously remarked, Dr. Liveing has recorded ("Megrim or Sick Headache, p. 329) that several observers have noted the pulse during an attack of megrim to be slow and of high tension (see fig. 37). And very soon after I found out the relation of this headache to uric acid, and the fact that by influencing the uric acid I could produce or remove the headache, I also noticed that when I altered the uric acid, I altered at the same time the rate and tension of the pulse, so that I eventually formulated the conclusion (*British Medical Journal*, January, 1889, p. 291) that, *cæteris paribus*, arterial tension varies with the amount of uric acid that is circulating in the blood," with the rider that, in so far as it depended on uric acid, it was in my power to alter it, in either direction.

I thus came to believe that uric acid not only accounted for the headache, but also for the high tension pulse and cold extremities that so often accompanied it, and that as uric acid obstructed the capillaries, and so raised the tension, it produced slowing of the pulse, in accordance with Marey's law that pulse rate varies inversely as arterial tension. Thus he says, "Le cœur bat d'autant plus frequement qu'il éprouve moins de peine a se vider," and then he goes on to explain that the chief obstacle to the heart's systole is the resistance "que le sang éprouve a s'ecouler des artères dans les veines a travers les petits vaisseaux;" and again he says, "La vitesse du sang augmente si la force du cœur augmente, ou si la resistance des petits vaisseaux diminue," and then he expresses the effect of the arterial tension, produced by the resistance in these little vessels, on the rate of the heart's action, by saying, "le cœur précipite ses battements à mesure que la tension arterielle leur fait moins d'obstacle." ("Circulation du Sang," pp. 315—336.)

Then as to the signs of "forte tension arterielle," he mentions "pulsations rares, le cœur se vide difficilement le pénétration du

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sang dans les arteres est lente—le dicrotisme n'a que peu d'amplitude ; " and again " Le resserrement des petits vaisseaux cause primitive de cette tension élevée des artères se traduit par le diminution du volume des extrémités par la moindre coloration des teguments, par l'abaissement de la temperature périphérique " [1] —in a word, all the signs of the uric acid headache and the conditions to which it is related.

If my premises are good, and my deductions sound, and if uric acid influences the circulation to the extent which I have thus been led to believe that it does, it follows that uric acid really dominates the function, nutrition, and structure of the human body to an extent which has never yet been dreamed of in our philosophy, and in place of affecting the structure of a few comparatively insignificant fibrous tissues in which it is found after death, it may really direct the development, life history, and final decay and dissolution of every tissue, from the most important nerve centres and the most active glands, to the matrix of the nails and the structure of the skin and hair.

If we turn to physiology, we find that the excretion of uric acid varies inversely as the acidity of the urine. Figs. 1, 2, and 3 serve to demonstrate this pretty completely, and as regards pathology and the action of drugs, anyone can demonstrate the same for themselves in a few hours' work such as that shown in fig. 3. Let them take a dose of citrate of potash, and as the acidity falls uric acid will rise, or let them take an acid, and as acidity rises uric acid will fall.

As regards physiology, the large excretion in the a.m. and early p.m. hours (fig. 3) has long been known, for Sir W. Roberts (" Urinary and Renal Diseases," p. 71) tells us that the quantity secreted during what he has called the alkaline tide, is three times as large as at other periods of the day, and those who have followed my description of fig. 3 will have seen that this is not due to any increased formation of uric acid in these hours, but to the previous storage or retention of uric acid in the tissues during the high acidity period of the previous night, and that the quantity of uric acid excreted on any given morning is proportional to this and to the fall in acidity of the urine. They have seen also that by altering the acidity of the urine, that is, the alkalinity of the blood, we can completely prevent there being any large excretion of uric acid in the morning hours.

Prev. ref. p. 549.

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But in physiological conditions there is always a large excretion of uric acid in the morning hours, and for reasons which I have given in the description of fig. 3, the uric acid which produces this large excretion has to pass through the blood on its way to the kidney, while conversely in the later p.m. hours there is always a low excretion of uric acid, and the blood is more or less free from it.

It follows from this and my previous arguments and deductions, that uric acid is present in excess in the blood during certain hours of each day, and more or less completely absent from it during certain hours of each evening and night (fig. 3).

Uric acid is therefore in excess in the blood daily from about 4.0 or 5.0 a.m. to about 2.0 p.m. (see figs. 2 and 3), and it is more or less completely absent from it from about 2.0 p.m. to midnight. There is occasionally a slight rise of uric acid above urea in the afternoon hours, often between 3.30 and 6.30 p.m., represented probably in fig. 3 by the slight falls of acidity at 5.0 p.m. and between 6.0 and 10.0 p.m., but this varies considerably with diet, exercise, and other factors, and need not now detain us.

But if arterial tension varies with the amount of uric acid that is circulating in the blood, and if, as Marey shows, the arterial tension or blood pressure controls the rate of the heart's action, it follows that the pulse in physiological conditions will be slower and of higher tension in the early a.m. hours and up to about 2.0 p.m., and quicker and of lower tension in the p.m. hours that follow up to about midnight.

My researches have left no doubt in my mind that this is the case, and I am confident that all clinical observers will uphold me in this statement, and Marey himself says: "On observe le matin au reveil un ralentissement du pouls avec tous les caracteres de la forte tension: le soir contraire le pouls s'accélère et présente le caractère de la tension faible." ("Circulation du Sang," p. 350.)

Again, if pulse rate is a measure of arterial tension or blood pressure, and this in its turn is, other things equal, a measure of the amount of obstruction of capillaries, it follows that the capillaries are most obstructed in the above-mentioned a.m. hours, and least obstructed in the p.m. hours.

And we have fairly abundant and independent evidence that this is the case, for, according to Marey, the distance which separates the temperature in the rectum from that in the mouth is a measure of the contraction of the vessels of the skin; the further these two temperatures are apart the greater is the contraction of

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the skin vessels and *vice versâ*, and we have seen in fig. 5 that these temperatures in physiological conditions are far apart in the a.m. hours up to 2 p.m. or rather later, and are much closer together in the p.m. hours that follow, proving that the skin vessels are relatively obstructed in the a.m. hours and relatively free in the p.m. hours, which is in absolute and complete accord with the physiological fluctuations in the excretion of uric acid as shown in fig. 3.

Then we have also independent proof that the capillaries are obstructed in these same hours in another important organ of the body, namely, the kidney, for fig. 3 shows in common with nearly all the excretion curves in this volume that the urine is scanty in the a.m. hours and up to 2 or 3 p.m., and tends to be profuse in the p.m. hours which follow.

But it has been pointed out that the flow of urine may be stopped by faradising the central end of the vagus nerve, which causes contraction of the renal vessels (*British Medical Journal*, "Epitome," 1895, p. 104), therefore contraction of the renal vessels diminishes the flow of urine and their dilatation increases it.

Therefore obstruction of renal vessels in physiological conditions is greatest in those hours of the day in which the excretion of uric acid most exceeds its normal relation to urea, and their obstruction is least in those hours of the evening and night in which uric acid is furthest below its normal relation to urea.

And in the case of the kidneys we have evidence that the renal capillaries are directly obstructed by uric acid in the blood, and this evidence places the possibility of there being any intermediate factor almost completely out of court, in the fact, already mentioned in the description of fig. 3 and elsewhere, that the urinary water actually varies from hour to hour and day to day throughout life, and alike in physiology, drug action, and pathology, inversely with the height of the uric acid above its normal relation to urea.

From which it follows absolutely that, as we can control the uric acid, we can also control the excretion of water by the kidney, and we shall see presently, and have already to some extent seen in chapters ii. and iii., that nearly the whole group of so-called diuretic drugs furnish instances of this law, and produce diuresis, and not diuresis only, but also altered blood pressure, pulse-rate, temperature, formation of urea and liberation of physiological energy throughout the body, by clearing the blood and urine of uric acid, and if for any reason they fail to clear the blood of uric acid, they also fail to produce any of these effects.

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But if uric acid diminishes the excretion of urinary water by obstructing the renal capillaries, it follows that drugs which act like it, such as digitalis or erythrophlæum, in contracting the arterioles and raising the tension, should also produce the same result. And I have been much interested, and have quoted in several papers from Dr. Brunton's researches with these drugs, which show that this is the case. Thus he says ("Pharmacology and Therapeutics," ed. iii., p. 430):—"Thus Mr. Power and I found that on injecting digitalis into the circulation of a dog the blood pressure rose, but the secretion of urine was either greatly diminished or ceased altogether. Here it is evident that the renal vessels had contracted so much as to prevent the circulation through the kidney, notwithstanding the rise that had taken place in the blood pressure.

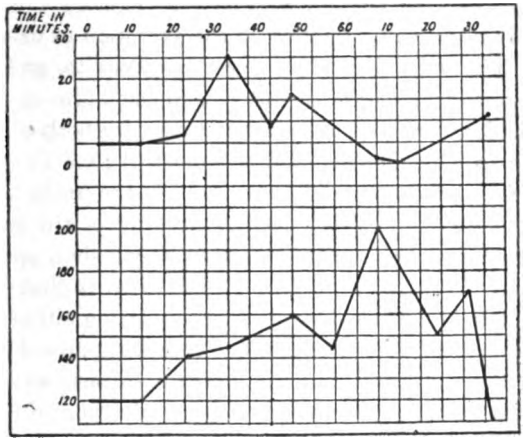

FIG. 32.—CURVES SHOWING THE EFFECT OF ERYTHROPHLÆUM UPON THE BLOOD PRESSURE AND SECRETION OF URINE.

(From Dr. Lauder Brunton's paper in *Phil. Trans.*, vol. clxvii.)

After a while the blood pressure began to fall, and then the secretion of urine rose much above its normal, showing that the general blood pressure was then able again to drive blood into the kidneys."

And Dr. Brunton's figure of the excretion of urine during the action of erythrophlæum, which he has most kindly allowed me to reproduce here, shows exactly the same thing (see fig. 32).

It seems that in the case of digitalis, and other drugs of similar action, the diuresis has been wrongly credited to the rise of pressure, which Dr. Brunton's figure and facts show that it does not completely

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correspond to. The first effect of these drugs is to hold back and retain in the body some water, and then, as the arterioles are relaxed and the blood pressure falls, this passes out, producing a marked temporary diuresis.

Digitalis and erythrophlæum thus exactly parallel what occurs in the uric acid headache, in epilepsy, hysteria, and other conditions accompanied by high tension pulse and obstructed capillaries. While the arterioles are contracted and the pressure high, the water is held back and retained in the blood and tissues, but later on when the capillaries are freed and the pressure falls, it passes out in a more or less copious diuresis, and urinary water is thus inversely as the uric acid excretion, and inversely as the obstruction of the capillaries.

Then again in chapter ix. we shall see that the capillaries of the lungs own to being obstructed in exactly the same way and in exactly the same relation to the excretion of uric acid that those of the skin and kidneys have already owned to, and what has been said about the excretion of water from the kidneys might apply almost word for word to that from the lungs, for both of these vary together, both in physiological and pathological conditions inversely with the height of the uric acid above urea in the urine.

These facts alone, to say nothing of the evidence from other tissues and organs which is also, as we shall see in other chapters, often very striking, suffice, I think to prove that high arterial tension or high blood pressure in man, occurring either in physiological or pathological conditions, is due to obstruction of capillaries throughout the body, and that the most important cause of this obstruction is the presence of a relative excess of uric acid in the blood stream. See also figs. 54 and 57 with the changes in the pulse rate and blood pressure there shown.

There are absolutely no facts against such an explanation of what has been observed, and there are hundreds of facts in its favour; for not only does it explain an almost numberless sequence of events in physiology and a still larger number in pathology, but it gives us a power to vary and control these events and sequences to which we were previously complete strangers.

Having arrived, then, at the conclusion that excess of uric acid in the blood stream produces obstruction of capillaries throughout the body, we may spend a few moments in considering the way in which it may produce this effect.

I have nothing definite to say on the matter, but think that we shall gain by keeping the more probable ways in our mind's eye, so

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that if we meet with anything pointing to one road rather than the other, it may not escape us.

(1) To make a beginning uric acid may act like digitalis, or erythrophlæum just mentioned, and these we learn from Dr. Lauder Brunton (previous reference, p. 996 and 273), act locally on the vessels of an artificial circulation, and in the case of erythrophlæum after division of the cord, so that all question of any action on the vaso-motor centre is removed.

(2) Then again it may act directly on and through the vaso-motor centre.

(3) And lastly, I think there is a third possibility, though so far as I know this has never been suggested by anyone except myself, and should it eventually work out it might come to very much the same thing as the local action theory No. 1.

It was suggested to me by watching day after day, as I have done for years, the extremely slow and tedious filtration of the gelatinous urate of silver through the abestos fibre filter as used in Haycraft's process for the estimation of uric acid (see chapter xviii.).

It occurred to me that if the capillaries of the body resembled in any way the interstices of that abestos filter, and if the uric acid was present in the blood stream in some similar gelatinous form, and if the heart had to shove it through those capillaries, it might have great difficulties in doing so and might occasionally, as we know occurs sometimes in pathological conditions, get the worst of the encounter.

In a word, it occurred to me that the obstruction produced by uric acid in the capillaries of the body might be mechanical and not vital.

To test the possibility of such a thing, I got some kidneys and tied a canula into the renal artery and measured the quantity of water or salt solution that poured out of the renal vein in a given time and under a given hydrostatic pressure.

I then added on to this solution small quantities of finely divided oatmeal, flour, mud, and other things, and watched their effect on the flow from the renal vein.

And lastly I got some gelatinous urate of silver, washed it free from chemicals, and added to it the solution passing through the kidney, and found that it had a far more powerful effect on the circulation than the other substances, as comparatively small quantities sufficed to stop almost completely the flow from the renal vein.

The condition in which uric acid causes obstruction of capillaries

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in the human body is one in which probably it is in solution in the normal phosphates of the blood stream, in which there are also probably present some alkaline salts of potash or soda; and we know that uric acid or urates, when in solution with phosphate of soda in a test tube, will, when cooled or treated with other chemicals, deposit in a similar colloid or gelatinous form; and it is quite possible that in the blood something of the same kind may occur just when there is a change of solubilities, or a balance, as it were, between alkalies on the one hand and acids on the other; and the action of salts of lithia, for instance, makes it practically certain that it is upon the neutral phosphates of the blood that the solubility of uric acid in that, and probably other fluids of the body, chiefly depends.

This condition of the blood, to which I propose for the sake of convenience in writing to give the provisional name *collæmia*, which will hence forward be used as equivalent to uricacidæmia, especially when I want to bring out the possible powers of urates in obstructing the capillaries, may be represented to the mind as much resembling a snow shower in the atmosphere, there the crystals come either one or two at a time, or in groups and batches now numerous, now scanty, or finally in a blinding storm, shutting out the landscape and promptly obstructing the roads and paths.

Such floating masses of colloid passing through the tiny blood paths must, even when not very numerous, by mere constant contact like floating ice in a river, very greatly hinder the capillary circulation, and there is no difficulty in believing that they may adequately account for all the phenomena of obstruction on the one hand, as seen for instance in the skin in migraine, and of high blood-pressure as measured in the radial artery on the other; and, as we shall see presently, they will account for several points in the connection of disease with the excretion of uric acid in the urine which are otherwise inexplicable.

Mr. J. E. Saul, F.I.C., who has very kindly at my request undertaken from time to time to examine the conditions affecting the solubility of this colloid uric acid has brought out some points which, if not entirely new, are well worth bearing in mind while we consider the question.

Thus it appears that uric acid or urates, in solution with phosphate of soda, will quickly throw down a bulky colloid precipitate if rapidly cooled, or if the solution is rendered faintly acid; a similar solution of alkaline urates does not give an immediate precipitate on cooling, but on addition of a little acid a colloid precipitate is at

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once thrown down. And this colloid precipitate is said to consist of a combination of acid urate of sodium and uric acid, the so-called quadriurate of Sir W. Roberts.

We see then that, speaking broadly, there are two things which will bring down colloid uric acid in the test tube, one is cold and the other slight acidification.

Now it appears probable that the acidification acts in the tube just as I have pointed out that acids act in the human body, *i.e.*, they convert a certain amount of the neutral phosphate of soda, which is a solvent of uric acid, into acid phosphate of soda, which is not a solvent, so that some of the uric acid is precipitated; and if this is so the effect of a given dose of acid will depend on the amount of neutral phosphate of soda it meets with in the blood just as I have also shown (again with Mr. Saul's help, see chapter ii.) that the effect of a given dose of lithia depends on the amount of phosphate it meets with.

It seems then as if there is a certain point at which there is a balance between acid on the one hand and alkali on the other, depending also somewhat on the quantity of phosphates present, when colloid uric acid tends to be thrown out in the blood stream just as in the glass test tube (*collæmic point*); but if, when this condition is present in the human test tube, you give an acid you get such a further and decided precipitation of uric acid that it is all caught up in the liver, spleen and fibrous tissues (gout), and the blood in general promptly becomes clear of uric acid just as we know that it is generally relatively clear in acute gout, and the urine now contains less than normal, and the blood-pressure falls because the capillaries are free. If on the other hand, when there is collæmia from a balance of alkalies and acids in presence of phosphate of soda, we give an alkali, the blood-pressure remains high and the urine scanty and full of uric acid, and this continues as long as an alkali is given, and as long as there is any uric acid to be dissolved in it; but if the uric acid comes to an end, the alkali being continued, then there is eventually a fall of blood-pressure and a diuresis.

This seems, on the face of it, as if the solubility in the blood formed an exception to that in the test tube, in that alkalies prevent the precipitation of colloid uric acid in the glass, and yet alkali in the blood does not lower the blood-pressure, but I think that this exception may be apparent rather than real, for if in a condition of collæmia we give an alkali, this may indeed dissolve up some of the precipitate in the blood, but as the action of the alkali is also to

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bring fresh uric acid into the blood from the liver, spleen and fibrous tissues, the reverse of the action of acids in driving it out of the blood into the tissues, the condition of collæmia may remain much as before until the supply of uric acid runs short, and then, as we know, the blood-pressure falls even though the alkali is continued as before.

As soon as the supply of uric acid runs short there is a diuresis in spite of the alkali being continued, just as there is a diuresis under salicylates as the excretion of uric acid is coming down.

The only evidence that I have that alkalies seem to have a solvent action in collæmia is that kindly given me by Dr. T. Wilson, of Wallsend-on-Tyne, who reports that his headaches have been cured by my diet, and that his own remedy for them was bicarbonate of soda when the attack was coming on, and this always gave relief in from five to ten minutes.

Acting on what he told me, I did try some bicarbonate of soda in the last slight headache I had some months ago, and it undoubtedly relieved me, but as I, without thinking, took it in a tumbler of warm water, I am still in some doubt whether it was the hot water or the alkali that did good, as both the heat and the alkali would, as we can now see, tend to prevent collæmia, and I have now so few headaches that it may be some time before I can test the point again.

I can, however, contribute an experience which, I think, throws some light on these points, for one day when I was taking an alkali and had got my urine almost continually alkaline, and feeling very well, as I thought, because I had little or no uric acid to get into solution with it in the blood, I chanced to take some rhubarb for lunch, and very soon after the meal was over I was surprised to be taken with a slight but quite distinct headache. I can only suppose that when on an alkali I was well, not because I had no uric acid in the blood, but because with plenty of alkali I was on the alkaline side of the collæmic point, and that then the rise of acidity after lunch, re-inforced by the acid of the rhubarb (see fig. 57), brought the blood to the neutral or collæmic point, causing a rise of blood-pressure and headache. And Dr. Wilson, it is interesting to note, regards acids as poisons, and records several instances in which the taking of vinegar, or some food mixed with vinegar, or an acid wine such as sherry seemed very distinctly to bring on an attack of headache. And it is quite possible that if the alkalinity of the blood is high, or he had been taking an alkali, the subsequent taking of such

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an acid would bring his blood to the collæmic point and produce a headache just as the acid of the rhubarb appeared to do in my case. And such a headache might be cured either by taking more acid to clear the blood of uric acid completely, or by taking an alkali to get away from the collæmic point in that direction.

Speaking of this reminds me that I have seen from time to time quite a number of patients who have asserted that a dose of an ordinary acid mixture brought on a headache, though a very much larger number have had their headaches prevented or cured by a similar mixture, and we can now see that the report of the minority may have been just as true as that of the majority.

I have also notes of one or two cases in which an attack of asthma was relieved by a dose of sodii bicarb, which is difficult to explain unless the above considerations explain it (see chapter ix).

In old times, when I had frequent headaches and much uric acid, alkalies used to produce headaches or make them worse, but it is possible that in those days I did not take enough alkali to combine with all the uric acid present and carry it beyond the collæmic point.

Further, if this is correct, we can at once see that the cause of the onset of headache or depression with very high blood-pressure in the early a.m. hours is the passage of the reaction from the acid tide of the night, with the blood clear of uric acid, through the collæmic point to the alkaline side of the record, which may coincide with plus alkalinity of the blood and very low acidity of the urine. And I am decidedly of opinion that the pulse is often slower and the blood-pressure higher about 5.0 or 6.0 a.m., in spite of being warm in bed, than it is an hour or two later, though the lowest acidity of the urine may not be reached till about 8.0 or 9.0 a.m. (see fig. 3).

Again we can see that the low blood pressure and soft pulse which result from continued muscular exercise may be due to the collæmia being dissolved by the plus alkali and increased temperature as well as to the lowered pressure produced by the increased area of circulation in the muscular tissues; and then when the exercise has ceased, and the acidity of urine is rising and the alkalinity of the blood is falling, we again get it passing through the collæmic point, and get the headache, depression, and high blood pressure of fatigue when there is enough uric acid available to produce severe collæmia.

Another point which it may explain is the value of getting the urine alkaline (with citrate of potash, for instance) in acute Bright's disease, as pointed out by Sir W. Roberts (Urinary and Renal

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Diseases, ed. iv., p. 436) for this will not only lower blood pressure by getting some of the colloid in solution, but it will also render the substance of the kidney alkaline, and so prevent the retention and aid the excretion of uric acid from it.

To test some of these points I recently gave in a case of chronic Bright's disease with high blood pressure and slow pulse enough citrate of potash to render the urine alkaline almost throughout the 24 hours; but this, even though continued for more than a week, neither increased the urine, lowered the blood pressure, or quickened the pulse, at least to any marked extent: while iodide of mercury subsequently given very distinctly quickened the pulse.

Most of these points require much further investigation, but there are now very many things which seem to show that collæmia may be the cause of high blood pressure, and as we shall see, this already serves to explain more or less completely several facts otherwise inexplicable. Thus there is no doubt that the uric acid headache is greatly relieved by warmth, such as sitting in front of a good fire or plunging the hands and feet in hot water and keeping them there, and it seems probable that the real explanation of this is the effect of the warmth in preventing the collæmia, just as the drink of hot water I have mentioned probably had the same effect, and this also is just the reverse of the effect of washing the hands in cold water in Raynaud's disease.

Some evidence that an alkali may possibly help to dissolve collæmia so long as there is not more uric acid present than it can hold in solution, is I think to be seen in the record of the cases of epilepsy in chapter vii. treated with an alkali by Dr. C. Mordhorst of Wiesbaden, as well as in his case, also there recorded, in which an alkali given to a gouty patient apparently produced epilepsy. (See also remarks on these cases and on the paper of Dr. Ackermann in the same chapter.)

Again, I have recently seen a patient who came from South America, and who said that while out there he was able to eat a large quantity of meat without harm; but that if he attempted to do the same in this cold country he suffered terribly from depression, and he had thus been obliged to take less meat in this country. Now, I think that as he ate a large amount of meat in South America he would certainly have a large amount of uric acid through his blood, but the warm climate might do a good deal to prevent collæmia; while in this cold climate, even if he got less uric acid passing through his blood, there might be more severe collæmia owing to the precipitating action of the cold.

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And I believe also that when there is much uric acid in the blood exposure to cold causes severe collæmia, and this causes such a paralysing effect on circulation and nutrition that the result is a depression of nutrition and metabolism all round. Hence, as I know, some cases of mental depression are much worse in the very cold weather. On the other hand, when there is but little uric acid available, cold acts as a stimulant, it raises the acidity of the urine, and lowers the alkalinity of the blood, clearing it of uric acid in the way that acids do, thus stimulating nutrition and metabolism, and causing the fires to burn up brightly; and this is probably the explanation of the now very generally recognised fact that those who live on a fleshless or uric acid free diet, feel the cold less and require less clothing in winter than those who take flesh constantly. Cold is a stimulant to the former, but as it helps to cause severe collæmia in the latter, the fires are put out by it, rather than stimulated. These considerations also help us to understand completely the great effects of cold on the nutrition of the skin and the important part attributed to this agent in the production of Bright's disease, by the late Professor Semmola.

Then I notice that Herz (*Wiener Klinik*, June and July, 1896) in an article abstracted in the *British Medical Journal* epitome, November 28, 1896, points out that the smallest vessels whose walls are not muscular pulsate more vigorously the greater the rigidity of the tubes connecting them with the heart, and argues from this that the degenerative processes cannot, as supposed by Gull and Sutton, begin in the smallest vessels, but must in them be secondary to changes in the arterioles and larger vessels.

But these points are entirely favourable to the possibility of mechanical obstruction in these smallest vessels that have no muscles, and the reaction of the pressure thus produced on the larger muscular vessels behind them giving rise to pressure and strain and eventual degenerative changes, but I shall have to refer to some of these points again.

Some most interesting points with regard to the solubility of uric acid in the blood have been brought out by Dr. C. Mordhorst, of Wiesbaden, by some researches published in an article: "Die Entstehung und Auflösung der Harnsäureverbindungen ausserhalb und innerhalb des Menschlichen Körpers" Zeitschr. fur Klin. Med. 32 Bd. H. 1, u. 2.

Thus he divides the urates with which we have to deal into two: (1) The spherical urate, which probably corresponds to the colloid urate, investigated by Mr. Saul, which has a spheroidal

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structure under the microscope, and the needle urate—the biurate or acid urate of sodium.

The spherical urate differs from the needle urate chiefly in containing more alkali, and it does not appear to be a definite combination, but contains more or less alkali according to the quantity available in the fluid in which it is dissolved or suspended.

The more alkali and the less uric acid it contains the more soluble it is; but if with any given alkalinity the saturation point is exceeded, the urate is thrown out in spheres, which are so minute as to be invisible at first, but which gradually combine into visible masses.

The spherical urate is thus suspended not dissolved; but the addition of a solution of sodium will cause it to pass again into solution, or on the other hand the addition of an acid or acid salt will cause it to be still further thown out of solution.

The longer the spherical urate has been in suspension the more difficult it is to redissolve it, and after it has been in existence for some time it begins to decompose into sodium and acid urate of sodium (needle urate).

If a solution of sodium is added to crystals of uric acid, spherical urate is formed, and becomes visible in suspension round the uric acid crystals; with excess of alkali the spherical urate then passes into complete solution.

The spherical urate in solution or suspension is that with which we have to deal in the blood and tissue fluids of the body; and Mordhorst does not find in the blood any urate having less sodium than the biurate (needle urate), such as the quadriurate of Sir W. Roberts, though he thinks that such a quadriurate may form a temporary stage in the change from acid urate to uric acid.

We thus get a perfect gradation by addition of alkali from uric acid, through quadriurate and acid urate up to spherical urate, and a corresponding change in the reverse direction from spherical urate to uric acid by the action of acids or acid salts taking alkali away.

Hence everything that increases alkalinity increases the solubility of uric acid, and everything that removes alkali or diminishes alkalinity diminishes its solubility, which is in absolute and complete accord with all my physiological results in the human body.

These results have been obtained by Mordhorst by placing uric acid or urates under the microscope, and acting on them with solutions of caustic alkali, salts, or acids, as the case may be.

When we have the spherical urate in solution its precipitation is brought about by over-saturation of the containing fluid, and this

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may be produced either by addition of uric acid, taking away of alkali, evaporation, or cooling.

Owing to defective circulation the fluids in the lowly vascular fibrous tissues and cartilages of joints tend (as Sir A. Garrod has already pointed out) to be less alkaline than other tissue fluids, but they will contain the same quantity of spherical urate as the blood.

The spherical urate in the fluids of these extra vascular tissues will therefore tend to be thrown out, partly on account of their diminished alkalinity and partly because in sedentary conditions the fluids are not moving much between and through the tissues.

This spherical urate is first thrown out in extremely minute particles, which, however, may unite and congregate into larger and larger masses many times the size of a white corpuscle. These increasing masses of spherical urate eventually get large enough to block the lymphatic vessels of the part and to give rise to stasis, pressure and pain, and this is, according to Mordhorst, the causation of an attack of rheumatism, and accounts for the local swelling and tension.

If the spherical urate is left for some time *in situ* the needle urate is eventually thrown out; but, as in rheumatism, there is often very soon a general rise of alkalinity, the spherical urate is redissolved again without, it may be, leaving any needle urate behind it; the needle urate can also take up alkali and pass back again into the spherical form.

In gout, on the other hand, the spherical urates remaining longer in suspension become more difficult to dissolve, and hence the needle urate is more likely to be thrown out; but it is the spherical urate which causes the local irritation and the tissue changes, and when the needle urate is thrown out the irritation ceases.

Mordhorst also believes in opposition to Ebstein that necrosis of tissue is entirely secondary to the throwing out of the spherical urate, and this subject he has treated of in another paper, "Zur Entstehung der Uratablagerungen bei Gicht," Virchow's Archiv., 148 B., 1897.

It is only possible to give here quite a short outline of these interesting results obtained with the microscope, and it is obvious how very favourable they are to the explanation I have given of my physiological results, and Dr. Mordhorst says in a letter I recently received from him: "I am convinced of the correctness of your opinion, that the uric acid is retained in the tissues of the different organs through an abnormally low alkalesence"; and further on he

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says: "I am of opinion that Sir William Roberts has made the mistake to believe the fluid parts of the body to be a simple solution of alkaline and neutral salts, whereas it is a solution the alkalesence of which is considerably reduced through the presence of acid salts (mono-natrum phosphate), a thing still more the case in the cartilage and tissue."

And it follows from Mordhorst's results above stated that the more alkali the phosphates of the blood and tissue fluids contain, the better will they hold the spherical urate (colloid urate) in solution; and this is in complete accord with what I pointed out some years ago in the *Medico-Chirurgical Transactions* (prev. ref.) that binatrum phosphate given with sodii carb. increases the excretion of uric acid, while if the same salt is given with dilute phosphoric acid, or even with a salt such as sulphate of sodium, it will cause no plus excretion of uric acid, perhaps even a diminished excretion.

It is also of the greatest possible interest to me that Dr. Mordhorst should have seen reason to suggest that the spherical (or colloid) urate could block the lymphatics, and thus give rise to some of the phenomena of rheumatism, as this is very close to my own suggestion first made in the third edition, that the same substance may mechanically obstruct the blood capillaries, and thus account for the phenomena of defective circulation and high blood pressure.

Among points of minor interest, Dr. Mordhorst lays stress on the influence of cold in throwing the spherical urate out of solution, and its bearing upon the causation of rheumatism locally in certain exposed tissues, and this also bears on the explanation I have for some years been giving of the limitation of Raynaud's disease to the skin and superficial structures of the thicker parts of limbs.

Dr. Mordhorst is a believer in the presence of uric acid in healthy blood, and thinks that von Jaksch and Klemperer, who found none, worked on too small quantities of blood (prev. ref. p. 21 of reprint).

He thinks also that blood can at times dissolve more uric acid than it can continue to hold in solution, and this is in favour of what I have said, that uric acid interferes with its own solubility in the blood, and is interesting in reference to the effects of alkalies previously mentioned, as they may, as I have suggested, bring a lot of uric acid into the blood, and when there may fail to hold it in complete solution and so produce collæmia and high blood-pressure, while some increase of alkali may dissolve up the colloid or spherical urate once more.

Dr. Mordhorst also points out that the effect of deficient circula-

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tion in the skin, whether produced by cold or other causes, is to make its fluids less alkaline, so that they become super-saturated with urates, and contain the spherical urate in suspension, and if this is so the defective circulation produced by collæmia will tend to keep up the collæmia, and hence in Raynaud's disease washing the hands in cold water may start a local collæmia, which tends to progress and requires a great change of general alkalinity to dissolve it up again.

I will now give a few more facts bearing on the relationship of urinary water to uric acid in excretion. Thus on May 8, 1891, uric acid was high, having a relation to urea for the whole twenty-four hours of 1 to 22. This means that there was a large excretion of uric acid, some 4½ grs. of it being washed out from deposits in the organs and tissues, and passing through the blood on its way to the kidney.

Now, practically, a large excretion of uric acid on any day means a large excretion in the alkaline tide periods of that day.

And now look at the urinary water on this day; with a large excretion of uric acid the water of seventeen hours of the day equalled only 600 cc., or 35 cc. per hour, a very low excretion; and during the seven hours of the night it was 570 cc., or 81 cc. per hour; the water held back during the day was, to a large extent, passed out as soon as the high acidity of the night period cleared the blood of uric acid (the exact parallel of digitalis).

Then take another day, as May 11, when the uric acid bears nearly its normal relation to urea, namely, 1 to 32; there would be but a slight excretion in the alkaline tide, and, in accordance with our premises, little or none passing through the blood; and, under these conditions, the water for seventeen hours of the day was 1370 cc., or 80 cc. in the hour; while the excretion in seven hours of the night was 630 cc., or 90 cc. per hour; on May 8 the urine per hour at night rose to two or three times its amount per hour in the day. On the 11th the night urine was only one-eighth more per hour than that of the day; on the 8th water was held back in the day and passed out at night; and on the 11th it was passed freely in both periods; hence, as I have said, the urinary water is inversely as the uric acid excreted along with it, and inversely as the amount of it in the blood, because the greater the amount of uric acid in the blood the more obstructed are the capillaries of the kidney.

It will thus be seen that my assertion that arterial tension varies directly as the uric acid in the blood has other foundations besides observations of the pulse rate and tension, though, as we shall see

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presently, these are conclusive enough, and followed from hour to hour the same thing is seen; the urinary water is inversely as the uric acid, and if the uric acid is intentionally increased or diminished the water alters in the opposite direction.

This brings me to the action of drugs and the experimental aspect of the question, but the same laws hold good.

(1) All substances which increase the solubility of uric acid increase its excretion and *vice versâ*.

(2) Substances which increase its solubility bring it into the blood in large quantity, obstruct the capillaries, slow the heart, and diminish the urinary water.

I have already gone into the action of drugs on uric acid: I shall here merely mention their effects as regards the pulse rate and tension, and the secretion of urine.

First of all, drugs which increase the excretion of uric acid; alkalies, as soda and potash, increase the excretion of uric acid and diminish the urinary water; but as their effect on uric acid is coming to an end (possibly because all the immediately available uric acid is cleared out) there is more or less diuresis, the water which they at first held back passing out. This is illustrated in the figures of May 8 just mentioned. This was a natural excretion (or fluctuation in excretion) apart from drugs, but precisely the same thing would have occurred if I had given alkalies to increase the uric acid.

Salicylates again bring excess of uric acid into the blood, and while the excess of uric acid is being passed in the urine, it is not very copious, but tends to be high-coloured and scanty; hence as has been noted by several observers (Huber in *Deutsch Archiv. fur Klin. Med.*, xii., p. 129, and Stiller, *British Medical Journal*, 1890, vol. i., p. 808), as well as myself, the great diuresis with salicylates comes on the second day of their administration, when the excretion of uric acid and the amount of it in the blood is beginning to diminish from want of supplies.

Diuretin = Salicylate of sodium and theobromine (= dimethyl-xanthin) appears to me to produce diuresis in much the same way that salicylate of soda produces it, namely, by clearing the blood of uric acid. I made some experiments with tabloids of this substance, kindly sent me by Messrs. Burroughs, Wellcome and Co., and my results show that just as with salicylate of soda there is no diuresis on the first day of taking the drug, on the contrary, the uric acid rises and the water falls, but there is a diuresis on the second or third day, when the excretion of uric acid comes down again. I

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have no doubt, therefore, that the diuresis is due to the salicylate element, or rather to the action of this element on the excretion of urates, and this explains the fact, noted by some observers, that the diuretic effects of diuretin may continue after ceasing to take the drug. (Massalongo and Silvestri, "Reforma Medica," March, 1893.) On the other hand, if the diuresis were due to the dimethyl-xanthin it would occur soon after the drug was administered, as is the case with uric acid, hypoxanthin, caffeine, &c. (see previous remarks on these substances).

It is interesting to note that diuretin has been said to diminish the area of cardiac dulness by exerting a tonic action on the cardiac muscle, and it is therefore proposed to give it in uræmia in place of digitalis, when there is a slow pulse (*Zeitsch. für Klin. Med.*, 1894), vol. xxii. As will be seen in chapter xiii., I have given salicylates in uræmic conditions with considerable benefit; but I should doubt very much whether either salicylates or dimethyl-xanthin have any tonic action on the cardiac muscle, and I believe that they reduce the area of cardiac dulness in the same way that iodides or mercury and other metals reduce it, by clearing the blood of uric acid, freeing the capillaries and thus allowing of a fall of blood pressure, which reduces the resistance to its action, and, therefore, the work the heart has to do. Probably caffeine, a near relative of theobromine, which is now a good deal spoken of as a cardiac stimulant and tonic, acts in exactly the same way.

With phosphate of soda again the water fluctuates in accordance with the excretion of uric acid, and independently of the amount of the drug; when the drug increases markedly the excretion of uric acid, the water tends to be low.

A large excretion under the phosphate or a salicylate is not, as I have remarked before accompanied by any headache, but the excess of uric acid in the blood keeps the capillaries moderately obstructed and pulse tension somewhat high, though to nothing like the same extent as would be the case if the same amount of uric acid was being excreted under an alkali; so that I have supposed that the compound formed by uric acid with salicylates and alkaline phosphates has less effect on the capillaries than the combination with a simple alkali, but probably even when salicylates or phosphates are in circulation there is always some urate combined with an alkali, and this may account for the effect on the capillaries in all cases.

Of drugs which diminish the excretion of uric acid, opium is perhaps the most important; I believe that it acts as an acid, which

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in nature, apart from drugs, is the most important factor. The pulse of opium well being and of the rebound next day are to be found in fig. 34.

The effects of morphine in raising the acidity and causing retention of uric acid are shown in fig. 15, and along with these go the quick low tension pulse, B in fig. 34, which again is the sign of a free capillary circulation throughout the body; its effects and further signs being mental well being, bodily strength and power of endurance, and a free excretion of urinary water. Here, again, all these effects are due to the action of the drug on uric acid, and correspond with it. Thus, one morning before breakfast when my pulse was slow and of high tension (rate 58), I measured the urine in the hour ending 8.15 a.m., and found it 53 cc., I then took ♏ vi. of tincture of opium, in tabloids, the pulse at 8.15 being 62, and I collected the urine of the next hour ending 9.15, no food or drink having mean-

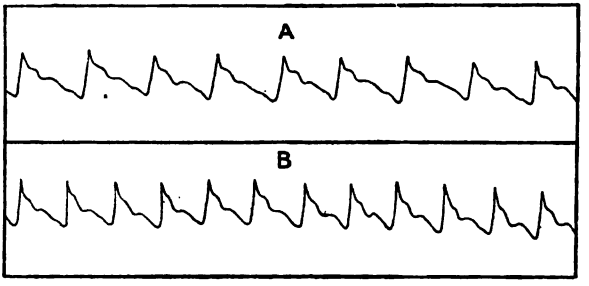

FIG. 33.—PULSE TRACINGS SHOWING THE BLOOD PRESSURE A BEFORE AND B DURING THE ACTION OF MERCURY.

while been taken since the previous evening. At 9.15 a.m. the pulse was 72, markedly softer, and with a larger dicrotic wave than the pulse trace at 8.15, and the urine passed in the hour was 234 cc. Obviously then the comparatively scanty urine at 8.15 a.m. was not due to want of water in the body, but to obstruction of the capillaries with which it corresponded; and the ordinary morning collæmia was here brought to an end by the action of the opium as an acid.

Mercury I have also written about, and as to the facts that it reduces arterial tension, and produces diuresis, the writings of Broadbent and Jandrassick sufficiently testify. I believe, as I have said, that these effects are simply and solely due to its action on uric acid, furnishing in this respect but a single instance of my

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general laws above stated. Fig. 33 shows the pulse tracing, A before and B during the action of mercury, the latter corresponding with a minus excretion of uric acid and diuresis (see fig. 17, p. 60).

Fig. 34 shows B the pulse of opium well being, the first stage action of opium; note the quick fall, and the small first wave, and the relatively large dicrotic wave. The capillaries are obviously free, and the pulse soft and quick; and with this the urine is profuse, as in the instance where a dose caused such marked diuresis in myself as mentioned above, and there is well being and increased mental activity.

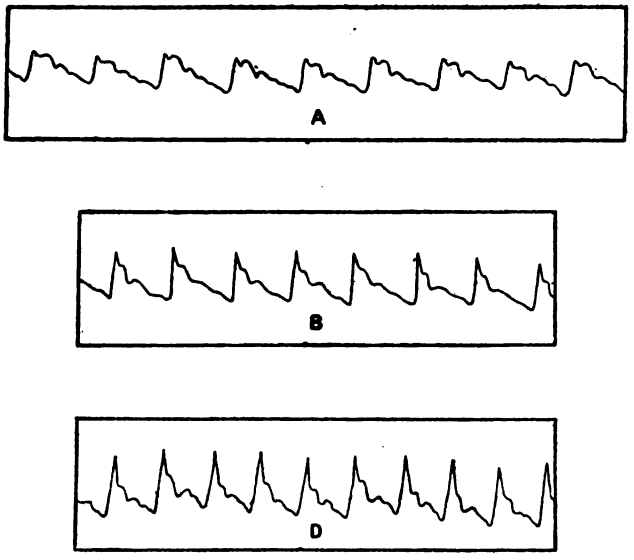

FIG. 34.—PULSE TRACINGS OF OPIUM REBOUND, OF OPIUM WELL BEING, AND OF ANTIPYRIN WELL BEING.

D shows a very similar pulse, produced by taking antipyrin, and both opium and antipyrin relieve the uric acid headache.

A is the opium rebound, second stage action of opium, the pulse of the morning hours after a dose of opium over night. Note the slow fall, the large first wave and relatively small second wave. With this there goes headache, mental depression, malaise, disinclination for exertion, and the urine is scanty and contains excess of uric acid, and the contrast between this pulse tracing and B and D is very marked.

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Fig. 33 shows that mercury produces a pulse like B or D, because it also clears the blood of uric acid, and it also cures migraine.

Lithia is one of the most interesting of the other drugs which produce the same results. I have given above, with reference to fig. 14, my explanation of the fact that it reduces the excretion of uric acid.

Lithia markedly diminishes the acidity of the urine, and yet, unlike the alkalies which produce this result, it reduces arterial tension, quickens the pulse, and produces diuresis. Here again we see that the effects on the pulse tension and flow of urine depend on the uric acid, and not on the acidity, alkalinity, or other power of the drug. Soda and potash raise the tension of the pulse and diminish the urine, while it becomes more alkaline. Lithia diminishes pulse tension and increases the urine, while it becomes also more alkaline, but soda and potash increase the excretion of uric acid. Lithia diminishes it.

Again, as before remarked, if all uric acid has been removed by a course of salicylates, soda or potash will fail to increase the excretion of uric acid, and in this case they will also fail to affect the pulse tension and the flow of urine.

The facts about lithia are very interesting, and I find on a reference to my old notes and curves that on a day when no drugs were taken the urinary water was 1280 cc., and there was a plus excretion of uric acid (1—24). On the following day 25 grs. of the citrate of lithia were taken, and with this there was, as is usual with lithia, a great fall in acidity of the urine, viz., to 38 grs. from 62 grs. on the previous day, but in spite of this uric acid was diminished greatly, having a relation to urea of 1—44. And now mark the result; if an alkali had been given, as potash or soda, to produce such a fall of acidity, a plus excretion of uric acid would have been the result, the pulse tension would have been high and the urine scanty, but lithia, for the reasons previously given in chapter ii., produced retention of uric acid, cleared it out of the blood, and in spite of the rising alkalinity there were free capillaries and a very marked diuresis. The urine of the day before the lithia with a plus excretion of uric acid was 1280 cc., that of the lithia day with a minus excretion of uric acid was 1790 cc. Here again we see that the freedom of the capillaries and the diuresis resulting depends not on the greater or less alkalinity, but on the greater or less amount of uric acid in the circulation, and lithia apparently prevents collæmia just as acids do by throwing a certain amount of

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phosphate of soda out of action; and possibly the non-appearance of these phosphates in the urine may account for the fall in its acidity.

It may be of interest also to remark that a somewhat similar fall in the acidity of the urine accompanies the diminished excretion of uric acid produced by iodides, and this suggests that the retention they produce which remains unexplained, may be the result of some effect on the phosphates of the blood, but so far as I can learn there are no known chemical facts to support this.

In contrast to lithia see the effect of other alkalies. On March 16, 1888, no drugs, urine 1410 cc.; on March 17, pot. bicarb. gr. xxx., urine 1400 cc.; on the 18th, pot. bicarb. gr. xx., sodii bicarb. gr. xx., urine 1170 cc., and with this fall in urinary water there was a plus excretion of uric acid.

Again, on May 19, 1887, with no drugs urinary water was 1670 cc., and uric acid to urea 1—32. On 20th, with 70 grs. of bicarbonate of potash urine was only 1260 cc., and uric acid to urea 1—26, *i.e.*, with a plus excretion of uric acid under an alkali the urinary water was reduced, which corresponds with the fact that in the natural plus excretion of uric acid in migraine the urine is scanty and bears out what I have said previously, that the urinary water is inversely as the uric acid excreted along with it.

The action of iron and lead is precisely the same; so long as they diminish the excretion of uric acid they free the capillaries and produce diuresis, but when their first action comes to an end uric acid is excreted in excess, and there are then high tension slow pulse, and scanty urine, just as in the opium rebound.

All other drugs which diminish the excretion of uric acid produce just the same results; as cocaine, antipyrin, the nitrites, and various salts of the mineral acids, especially sulphates. Strychnia also (possibly indirectly) raises acidity and affects uric acid, and the pulse and urine, like other members of the group.

Fig. 22 shows us the effect of copaiba, the diuretic action of which is so well known, and we see that the diuresis it produced corresponds with a marked fall in the excretion of uric acid, so that no doubt the capillaries were freed. I believe that this may be taken as a type of a number of resinous substances which produce diuresis, and all of which probably act in the same way. Thus copaiba introduces a considerable quantity of copaivic acid in its resin which forms glycuronic acid in the system, and one or both of these acids may no doubt affect the neutral phosphates of the blood and prevent their being good solvents of uric acid. Tar,

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again, contains several acids. Rhubarb contains chrysophanic acid, and cannabis indica contains a resinoid substance, cannabin, which, like the resin of copaiba, may consist of acids. All these substances act as stimulants, causing free capillaries well being, and more or less diuresis, and all these effects correspond in time with a diminished excretion of uric acid in the urine. Tar is a stimulant, and in the form of a patent medicine which I have used, it undoubtedly causes marked well being and freedom of capillaries.

It is interesting to remember its value in lung troubles, as bronchitis and phthisis, and if it acts on uric acid it will no doubt free the capillaries all over the body, and be of use in lung troubles in the same way that the iodides are; and tar water is, I believe, one of the constituents of Hair's Asthma Cure, in addition to an iodide, the action of which it will no doubt increase.

Liquorice is another substance which has been used for many years in bronchitis and catarrh, and its action as a stimulant is referred to by Dr. Keith ("Fads of an Old Physician," p. 77), though I cannot quite agree with his pathology of headaches, sleeplessness, and low spirits; but liquorice, I have very little doubt, contains some resin or acid similar to that of tar or copaiba, and its solution in distilled water distinctly reddens litmus, and this no doubt accounts for its stimulant effects.

Rhubarb, again, has a remarkable stimulating effect, causing freedom of capillaries and well being, and its valuable stimulant action in gouty dyspepsia is, I think, probably due to its effect on uric acid.

Cannabis indica is a still more marked instance of the same thing, and its stimulation is very clearly contemporaneous with a diminished excretion of uric acid. Its stimulating powers are great, and it is well known to cure or prevent migraine, the uric acid headache.

In the same way, also, it is very useful in melancholia, mental depression and bad temper.

Like tar, it is useful in asthma and phthisis, and another drug with a similar action, the American spirit weed (Lachnanthes) has also been strongly recommended for phthisis, and it also appears to raise the acidity and clear the blood of uric acid, causing very marked well being.

Cannabis indica has also been strongly recommended as a hæmostatic in menorrhagia and this is extremely interesting, as we shall see later on that drugs such as mercury and iodides, which have the same effect that cannabis indica has on uric acid, are often

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very useful in hæmoptysis, when they probably act by lowering the blood pressure: but about this I shall have more to say presently.

If we only bear in mind the fact that clearing the blood of uric acid means freeing the circulation and quickening combustion and metabolism throughout the body, we shall have no difficulty in understanding how many of the drugs mentioned above effect at one and the same time, such different organs and tissues as the skin, the brain, the lungs, the stomach, the kidneys, and the uterus.

This shows up also very clearly the nonsense that is often talked about diuretic drugs and their action on the renal epithelium, it is easy to demonstrate that they have a similar and contemporaneous action on the epithelium and cells of every gland and tissue of the body, and this is due to the fact that they clear up collæmia and allow of a free capillary circulation also throughout the body; hence the corresponding fall in blood pressure and the size of the radial artery.

If now we turn to pathology, we again find a whole series of facts which our knowledge of the effects of uric acid on the capillaries will enable us to explain completely.

There are few clinical facts which are better attested than that having to rise one or more times in the night to pass urine is a very common symptom in Bright's disease, but it will, I think, presently appear that this is not so much a symptom of Bright's disease as of a condition (high arterial tension), which is very commonly present in Bright's disease.

When a patient tells me that he has to rise one or more times in the night to pass water, I feel sure that he has high tension (provided of course, there is no local irritation in the urinary passages), but this may or may not be due to Bright's disease.

As we shall see further on (chap. xiii.) the high tension of Bright's disease is almost certainly due to uric acid, that is, a patient with Bright's disease suffers from chronic uricacidæmia, but it is equally certain that a patient may have uricacidæmia without having Bright's disease, hence nocturnal urination does not necessarily imply Bright's disease.

The excretion in my own person on May 8, previously mentioned, will very well illustrate what I mean. On this day there was marked uricacidæmia in the alkaline tide, and the urine during the day was only 35cc. per hour, but at night the acidity rose, the uricacidæmia came to an end, and the excretion of water rose to 81 cc. per hour. Now, something of this kind happens in the high tension of Bright's disease every day; there is chronic uricacidæmia, but

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this is most marked in the alkaline tide of the morning, when the slow pulse is at its slowest, and the hourly excretion of water is at its lowest, and the temperatures in the mouth and rectum are at their furthest distance apart. It is least marked in the acid tide of the night, when the pulse is at its quickest and the hourly excretion of water at its highest; hence the patient with high tension, whether he has Bright's disease or not, has to rise in the night because he excretes much more water per hour at that time; and in my own case I have, under conditions similar to those of May 8, been roused up in the early hours of the morning by a distended bladder. Under the opposite conditions eight or nine hours may easily pass without micturition being necessary.

(For a case in which the hourly excretion of urinary water was much greater in the night than in the day in association with slow, high tension pulse, see article on "Obesity Treated by an exclusively Nitrogenous Diet and copious Libations of Warm Water, by Thomas D. Savill, with remarks on the excretion of uric acid, by Alexander Haig."—*Lancet*, 1893, vol. ii., p. 133).

It is generally possible to tell, when the urine is scanty, whether this is due to concentration of the blood, or to obstruction of capillaries preventing outflow of water from it (see effects of opium previously mentioned).

When it is scanty, owing to concentration of the blood, then there is no diuresis at night, but the water of the night hours is as scanty as that of the day. On the other hand, when it is scanty during the day, owing to collæmia and retention of water in the blood, it is profuse at night, when in the natural order of things the blood is cleared of uric acid and the capillaries are free, for all the water held back in the day rushes out; and this is well seen in that exaggeration of normal conditions, chronic morbus Brightii; here the urine is scanty, and the blood dilute during the day, while collæmia and consequent obstruction of capillaries are greatest; and the urine is profuse and the blood becomes concentrated during the night, when the collæmia, just as in normal conditions, is less, and the vessels are relatively free.

Supposing that under pathological conditions the plus uric acid in the blood continues all night, as sometimes occurs in the uric acid headache, then the water is scanty all night also; but we have abundant evidence that it is not scanty owing to concentration of the blood, in the diuresis, which occurs as the headache passes off.

Under opposite conditions, when the blood is really concentrated,

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the urine is as scanty by night as by day, and the following is an instance :—

On 18th March I took a long bicycle ride, and being out of training I perspired very greatly and found it very hot work; the urine on this day was 920 cc. (on the previous day 1230 cc.), = 40 cc. per hour in sixteen hours of the day, and 35 cc. per hour in eight hours of night. On the 19th it was 900 cc., 35 in the day and 42 in night. On 20th, 1030 cc., 39 in day and 50 in night, and on 21st, 1370 cc., 45 in day and 80 in night. It had now returned to nearly normal quantity, and the urine per hour at night was, as is frequently the case, nearly double that of the day. On the other hand, when the blood was concentrated, the water per hour at night was less, or not greater than that in the day.

When the blood is thus concentrated there is great thirst, but when the urine is scanty, owing to collæmia and obstruction of

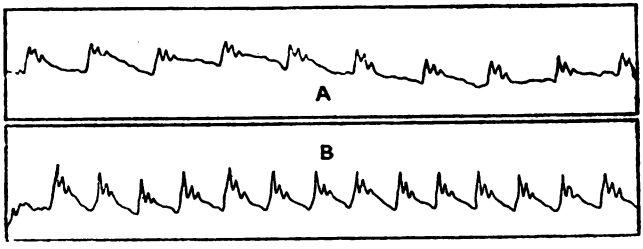

FIG. 35.—PULSE TRACINGS OF HIGH BLOOD PRESSURE IN BRIGHT'S DISEASE AND OF THE EFFECTS OF DRUGS UPON IT.

capillaries, there is an absolute distaste for fluids. Hence it is very common for those who suffer from chronic collæmia and high blood pressure, as in chronic Bright's disease and conditions bordering on it, to say that they are never thirsty.

With regard to the slow high tension pulse of Bright's disease, it is not only slowest and of highest tension at those hours (alkaline tide) when the excretion of uric acid is normally greatest, and quickest and of lowest tension in the acid tide of the night, but it is in our power to alter it, to quicken its rate and reduce its tension by the use of any of the drugs which diminish uricacidæmia just as in the case of the temporary uricacidæmia of a headache. Thus, in some cases of Bright's disease, where the pulse was slow, I have been able to nearly double its rate by influencing the uric acid, see fig. 35, where A shows a very high tension pulse, rate 52, and B,

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the pulse of the same patient ten days later, when drugs had had time to act, rate 80; and when several years ago there was some writing in the journals about the value of opium in nephritis, and in uræmic convulsions, I tried opium in one or two cases of Bright's disease, and where, in these cases, the pulse was slow, it invariably quickened it and increased the urinary water, and appeared to me to do good, though in cases of nephritis I have generally preferred to use acids or drugs which act in the same way, such as the iodide of mercury, to affect the uric acid, rather than opium, but in those cases of Bright's disease where mercury cannot be given on account of its at once producing salivation, the use of a little opium, especially if given with salicylates, should not be forgotten, and this combination of drugs, it is interesting to remember, is often of great use in the nearly-related disease, diabetes.

It may interest those who have not a laboratory at their door, if I say that the main characters of the high and low tension pulse can be demonstrated by means of a Higginson's syringe, a few feet of soft rubber tube just large enough to fit over the nozzle of the syringe, and a screw clamp. Fill the syringe and tubes with water, and screw up the clamp so that the water can only run out very slowly from the end of the tube; adjust a sphygmograph over the tube between the syringe, which with a muscular hand outside it represents the heart, and the clamp, which represents the more or less obstructed capillaries. When all is ready set the clock-work of the sphygmograph in motion, and work the syringe regularly by the second hand of a watch. If the clamp is much screwed up, you will get a slow diastolic fall, the secondary waves being nearly obliterated. If it is open so that the water passes easily you get a quick diastolic fall with large secondary waves, as in the dicrotic pulse. If the finger is placed over the tube instead of the sphygmograph, you will be able to appreciate the difference between an artery which is full between the beats and one which is empty.

While speaking of physics and mechanics I will mention also the arteriometer, invented by Dr. G. Oliver, and produced by Mr. Hawksley, the well-known instrument maker; because it seems to me that it is of very considerable value to me in aiding the clinical demonstration of the effects of uric acid on the circulation.

I must here, however, only mention the most important points, and refer my readers to Dr. Oliver's work[1] for further information.

[1] "Pulse-gauging," by G. Oliver, M.D., F.R.C.P. H. K. Lewis, London, 1895.

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The arteriometer professes to measure the distance traversed by a button in passing from one side to the other of any exposed artery, as the radial, in obliterating it; that is to say, the diameter of the artery.

The fact that the artery is obliterated is recorded by the finger of the observer, which notes the point at which pulsation ceases on the distal side of the instrument.

To make a long story short, it is found with this instrument that the greater the blood pressure the larger is the diameter of the radial artery, and though Dr. Oliver has invented another instrument for measuring pressure as apart from change of diameter, as diameter practically varies with change of pressure, the arteriometer is alone sufficient for most of the purposes that I have in view.

The clinical value of its record may be best shown by giving an instance. Thus we may say of a patient that his pulse was slower and of higher tension in the morning hours, and quicker and of lower tension in the evening hours; but with the arteriometer we may be able to say that his pulse in the morning was 55, and his radial diameter 2·0 millimetres, and in the evening his pulse was 65, and his radial diameter 1·5 millimetres.

Dr. Oliver goes into the effects of posture (sitting, lying and standing) on the calibre of the radial artery,[1] and has found them very constant, but it seems to me that he does not completely work out the causes of the changes produced by posture, and certainly he says nothing about the force of gravity, to which, I believe, they are really due.

On ordinary physical principles it appears that blood, like other fluids, will travel more quickly down hill than up—that is to say, will go better with gravity than against it, and the sphygmograph, as has no doubt long been known, tells us that this is so with our own circulation.

Take, for instance, a pulse tracing when sitting or standing with the wrist on the level with the head; gravity is here acting against the circulation, 1½ or 2 oz. pressure will be quite sufficient to develop the tracing which will show the ordinary signs of low tension.

Next take a tracing with the wrist on a level with the apex of the heart, here gravity is acting slightly with the circulation, in so far as the arteries of the arm are below the level of the aortic arch; it will now be found, perhaps, that 3½ oz. are required to develop the tracing which shows moderate tension.

[1] Previous reference, p. 13.

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And, lastly, bending forward, sink the wrist down between the knees, so as to increase the force of gravity; it may now take 5 oz. pressure to develop the tracing, which will show high tension.

Now, do exactly the same with the arteriometer. With the wrist on a level with the head it will read ·5 m., on a level with the heart, 1·1 or 1·2 m., and between the knees 1·5—1·6 m. Of course the absolute diameter will vary with the person, but these are average readings on my own radial.

It follows from this that the changes of calibre noticed by Dr. Oliver, in different postures, are the simple results of the various effects of gravity on the circulation in these positions.

Thus, with the wrist at the level of the heart, or, as Dr. Oliver advises, about 2 in. or less below it, it is obvious that in the sitting or standing posture gravity acts with the circulation, because the radial artery is below the aortic arch, and in the recumbent position gravity is neutral, because the radial artery is on the same level as the aortic arch.

Hence in the recumbent position one best gets the effect of the blood pressure on the artery pure and simple, but in clinical observation it is a very valuable thing to have a constant force like gravity at one's disposal, which one can add on to or take away from the blood pressure at pleasure, because this constant force will obviously produce greater effects the less the original distension of the arteries, and smaller effects the greater the original distension.

For, on the well-known principle that a candle added to the sun produces no visible effect, while a candle brought into a room from which the sun's light is excluded, produces very great effects, the addition of the constant distending force gravity, to a vessel whose walls are already greatly distended by high blood pressure will produce little or no effect; but the same force of gravity applied to a vessel whose walls are relatively lax from low pressure will produce quite a large distending effect.

It follows from this that the higher the blood pressure the less will be the variations induced by change of posture, and the lower the blood pressure the greater these variations, and this I find to be the case.

Thus the diameter of my radial artery is generally greater in the morning and less in the evening, and the postural variations are less in the morning and greater in the evening, and the following are common readings:—Morning, sitting, radial diameter 1·2, lying 1·1; evening, sitting, radial diameter 1·0, lying 0·8.

We can now understand completely Dr. Oliver's observation on

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p. 14, where he says:—"As a rule as years advance beyond the middle period of life the range of postural variation becomes gradually lessened, and it may thus mark the progress of physiological arterio-sclerosis, until the calibre may at last become quite uniform in posture."

For "physiological arterio-sclerosis" I should prefer to read physiological (? pathological) collæmia, and the causation of this depends in the most simple manner on our first principles, for every man on ordinary diet stores in his body during his youth and prime a large amount of uric acid, and as he begins the decline of life this is got into solution and passed through his blood, causing, as we know, high blood pressure; and this in its turn is the cause of the fact observed, the gradually lessening variations in the diameter of the arteries from change of posture, in accordance with the rule worked out above.

Doubtless the high blood pressure and the blocked, obstructed, vasa vasorum, are between them the cause of the arterio-sclerosis, a pathological change which quickly supervenes upon the physiological collæmia.

It is of the very essence of my argument in this volume that this physiological collæmia can be diminished or controlled by altering the diet, and that when this has been done its pathological effects will be diminished and postponed, and chief among these effects is that gradual failure of combustion, metabolism and nutrition, which we call chronic Bright's disease, as it is a mere prolongation or accentuation of the diminished combustion which is the result of all collæmia. This is seen in its simplest form in the fall of urea as the result of exercise in those who have plenty of uric acid available for collæmia, and in its most severe form in the fall of urea, and the excretion of unmetabolised albumen in its place in acute Bright's disease; in the physiological condition the removal of the collæmia by mercury or its prevention by diet, suffice to prevent the fall of urea, and it is replaced by a rise; in the pathological condition the same metal, if it can be got to act, will very soon reduce the albumen to a trace and send up the urea to a corresponding extent, increasing it by tens or even hundreds of grains.

It seems to me that the arteriometer will be of the greatest value in demonstrating the effects of uric acid on the blood pressure, and so on the diameter of the vessels. With many drugs it is now quite easy to get definite and distinct results, which can be recorded in figures, and some of which I shall mention further on; and in disease processes connected with changes of blood

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pressure we shall learn infinitely more about cause and effect if we can measure it more accurately.

In epilepsy the pulse is often slow and of high tension just before the fits, and I have suggested that high arterial tension is the actual cause of the fits, and in the case of epilepsy I have shown that this condition of pulse corresponds with an excessive excretion of uric acid, and probably with more or less marked collæmia. The urine excreted at the time of a fit is also scanty, and of high specific gravity.

In uræmic convulsions I have pointed out Sir W. H. Broadbent's opinion that the high tension is the cause of the fits, and in writing of Bright's disease I shall have to point out that the blood in that disease has been proved to contain excess of uric acid, and that it is easy to explain the fact, so that uræmic fits or the high tension which produces them may be, just as in ordinary epilepsy, due to uric acid.

Probably the same explanation may be applied to puerperal convulsions, as the fits come at a time, as I have elsewhere said, when some uricacidæmia is almost certainly present (*Brit. Med. Journ.*, Feb., 1889, p. 290; also previous remarks about the effects of menstruation, pregnancy, &c.) and the value of milk diet in preventing eclampsia is now very generally recognised (see *Charpentier Sem. Med.*, 16 Sept., 1896), and this quite coincides with my own experience, as I have had under my care from time to time a considerable number of pregnant women suffering from Bright's disease, and these being placed on a milk or uric acid free diet for some months before delivery have all done perfectly well, without giving any sign of convulsive troubles.

In mental depression and melancholia, as we shall see presently, Sir W. H. Broadbent has pointed out that the pulse is often slow and of high tension, while I have shown that these conditions are often associated with an excessive excretion of uric acid, and more or less uricacidæmia, and that they may be relieved or cured by affecting the uric acid.

The fact on which I have laid so much stress above, that the urinary water varies from hour to hour or day to day, and in physiology as well as in pathology, inversely as the uric acid excreted along with it, seems to me to afford absolute and irrefragable proof of the action of uric acid on the capillaries.

That the urinary water varies inversely as the uric acid, anyone who will trouble to estimate the excreta for a few days can easily convince himself; and it does so because an excess of uric acid

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over urea in the urine comes from an excess of uric acid in the blood, and an excess of uric acid in the blood (collæmia) obstructs the capillaries and diminishes the excretion of water, just as we have seen that digitalis and erythrophlæum do; therefore obstruction of capillaries is directly as the uric acid in the blood (Q.E.D.).

Obstruction of capillaries is not directly as any of the drugs used to affect uric acid, as these act quite differently in accordance with the amount of uric acid that is present for them to act upon: thus an alkali given to a gouty person will cause high tension and severe depression; but remove the uric acid beforehand with a salicylate and it will cause none. Lithia produces no depression and allows of a free flow of urine; soda and potash cause depression and scanty urine; they all render the blood more alkaline and the urine less acid; but lithia clears the blood of uric acid, while soda and potash produce uricacidæmia and collæmia.

I have just said that the obstruction of the capillaries varies directly as the uric acid in the blood, and pulse rate according to Marey is inversely as arterial tension, which is the result of capillary obstruction; therefore, pulse rate is inversely as the uric acid in the blood.

Now this brings me in contact with a subject about which a good deal has been written, namely, bradycardia, or slow action of the heart; and Prof. Reigel, from whom I have quoted elsewhere, divides bradycardia into physiological and pathological, and a close investigation shows that in all the conditions he speaks of there is uricacidæmia, which obstructs capillaries, and the bradycardia is due to this, in accordance with Marey's law.

In the physiological group come (1) the bradycardia of ten to twelve days after confinement; (2) that of conditions of hunger; (3) that of individual peculiarity.

After confinement, as I have pointed out elsewhere (*British Medical Journal*, Feb. and Nov., 1889), there is almost certain to be collæmia, because there is an interruption of digestive and other functions at the end of a period of active nitrogenous metabolism (pregnancy), and these facts probably explain also the causation of puerperal convulsions.

In certain conditions of hunger, also, there is a fall of acidity and temporary collæmia.

As to individual peculiarity, Prof. Reigel himself suggests that it often means some unrecognised disease.

In the pathological group come bradycardia of

(1) Convalescence from acute disease.

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(2) Diseases of digestive organs.
(3) ,, respiratory ,,
(4) ,, circulatory ,,
(5) ,, urinary ,,
(6) Intoxications.
(7) Diseases of blood and general nutrition.
(8) ,, nervous system.
(9) Other diseases.

Of (1) Acute diseases and the way in which they bring about collæmia, I shall have to speak very often (see chapter viii.), but I will just mention here that I have no doubt that the free capillaries and dicrotic pulse of fever are due to the clearing of the blood of uric acid by the rising acidity which fever produces. The pulse of fever often much resembles that produced by the nitrites which I have suggested is due to the same cause, a rise of acidity, but it follows from my first principles that a rise of acidity clearing the blood of uric acid causes retention of uric acid, and this retention will be followed, as in the case of opium and other drugs, by a rebound and plus excretion; that is to say, as the fever comes to an end and the acidity falls, the retained uric acid will be dissolved out and flood the blood, we shall have more or less severe uricacidæmia according to the amount retained, and slow high tension pulse (post febrile bradycardia), subnormal temperature, &c., in proportion to it. Hence a knowledge of the effects of uric acid enables us to explain the pulse conditions both in fever and convalescence, and to see that the pulse of the latter is the necessary sequence of that of the former (see p. 23).

With regard to changes in the rate and rhythm of the heart, Marey says that while they are often attributed to nervous influences, they are in not a few cases really due to pressure changes in the vessels either of the systemic or the pulmonary circulation (prev. ref., p. 484).

Writers on this post febrile bradycardia have observed that it is often met with in its severe forms in those who before the fever were strong and healthy, and yet in apparent contradiction they go on to attribute the bradycardia to weakness of the heart muscle.

Why should those who were previously strong and healthy have the weakest hearts after a fever? There is no doubt, however, that those who are strong and robust had the largest nitrogenous metabolism both before and during the fever; they would, therefore, store most uric acid and have the most severe collæmia after the fever, and the bradycardia would doubtless be in proportion to this.

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As regards the heart, the only necessary quality for the production of bradycardia is that it shall be sufficiently strong to withstand the strain which collæmia, obstructed capillaries, and high arterial tension put upon it, and this power is, to my mind, much more likely to be met with in those who were previously strong and robust; but if the heart fails before the high tension, we shall get palpitation or a quick, irregular pulse in place of a slow one, and some cases of tachycardia are no doubt thus accounted for; and in such cases the importance of giving drugs, such as morphine or mercury, that lower blood pressure, should be borne in mind; and as the pressure falls the heart will slow towards the normal rate (see also effects of chloroform and nitrites in chapter viii.). Thus a very interesting case was mentioned at a recent meeting of the Clinical Society (*British Medical Journal*, 1897, vol. 1, p. 144), where paroxysmal tachycardia came in sudden attacks in a child and was associated with enlargement of the heart. And the possible relations between such a condition and that of Grave's disease, about which I have already spoken, are most interesting. Further, I would most earnestly caution those who wish to arrive at the truth about these matters not to be too ready to attribute either bradycardia or tachycardia to any nerves or ganglia, or to refer the benefit obtained from such drugs as valerianate of zinc or morphine to their action on such ganglia, till the possible presence of collæmia and high blood pressure, and the by no means remote possibility that these drugs have cured by relieving it, have been considered.

(2) Digestive disturbance generally entails a fall of urea and acidity and uricacidæmia, and this is the common occasioning cause of the uric acid headache, also of fits, mental depression, fatigue, asthma, glycosuria, anæmia, and albuminuria; all of these are frequently found associated with dyspepsia or gastro-intestinal upset because these are, as we shall see in chapter x. the cause of the collæmia, but the collæmia once it has come into existence also tends to make the dyspepsia worse or to keep it going.

(3) Respiratory disease may entail deficient oxidation, and that, as I have pointed out in chapter iii., pp. 83 and 84, means a fall of acidity and consequent collæmia.

(4) Circulatory disease may obviously cause collæmia in several ways.

(5) Among the urinary diseases mentioned by Prof. Reigel, nephritis bulks largely, and of this and its collæmia I shall speak in chapter xiii.

(6) Intoxication by lead, alcohol, digitalis, and bile are specially

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mentioned, and the action of lead and alcohol on uric acid I need not go into again. Digitalis acts in accordance with the same law, and slows the pulse by contracting the arterioles and raising the blood pressure. The digestive disturbances that accompany jaundice are probably sufficient to cause collæmia, and jaundice is not always accompanied by a slow pulse, which points to the action being indirect.

(7) I shall only have to mention anæmia or leucocythæmia in reference to what I say in chapter xii. of the collæmia that occurs in relation to them.

(8) As regards the nervous system I admit that certain central irritation may contract the peripheral arterioles, raise arterial tension, and produce bradycardia, but I believe that disease of the nervous system more often acts indirectly by producing nausea, vomiting, or gastric disturbance with secondary collæmia and its resultant bradycardia (see previous remarks and quotation from Marey).

Under (9) are grouped fatigue, sunstroke, severe pain in various organs, and I should have no difficulty in proving that these may be accompanied by collæmia, and I shall speak of fatigue in connection with the causation of mental depression, chapter viii.

Severe pain, especially when connected with any of the abdominal or pelvic organs, causes more or less complete arrest of digestion and absorption of food; it thus brings about increase of the alkalinity of the blood and collæmia just like any other digestive disturbance; but whether this accounts for the effects of all pain, fright, &c., in producing shock and collæmia I am not prepared to say; but certainly in many of these conditions much good may be done by clearing the blood of uric acid, and I mentioned above a case in which this was done by the natives of Morocco by means of a dose of urine.

With regard to fatigue I will just remark, in passing, that while drugs which clear the blood of uric acid and promote a free circulation in the nervous and muscular tissues, such as morphine, cocaine, acids, &c., produce, as they are well known to do, feelings of mental well-being and bodily strength, and greatly increase the powers of endurance, it is extremely likely that drugs and physiological or pathological conditions which increase the uric acid in the blood, and so hinder the circulation through these tissues, will produce fatigue, or a condition on which it easily supervenes.

With reference to sunstroke, we may bear in mind that external heat produces uricacidæmia (see remarks n fig. 4), and some of the

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symptoms of this trouble may be due to high blood pressure and others to defective combustion, in a word, fatigue with special variations (see chapter viii.).

From the causation of bradycardia by uric acid in accordance with Marey's law we pass without difficulty to the causation of angina (see chapter xiv.), and of syncope (see also *Brain*, Spring Number, 1891, p. 88). Acute dilatation of the heart and other effects of high tension and the value of nitrites and mercury in such conditions is easily accounted for. I give here, fig. 36, a tracing showing an intermission in my own pulse when the heart was labouring against the high tension of collæmia, and I have suggested that epilepsy may in some cases be due to heart failure from this cause.

An interesting form of syncope is that which occurs during bathing, and it no doubt accounts for the loss of many lives every year.

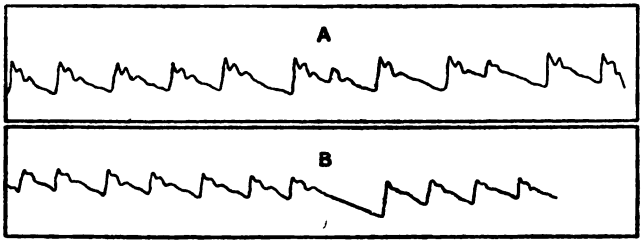

FIG. 36.—PULSE TRACINGS OF HIGH BLOOD PRESSURE. (A) FALTERING. (B) INTERMITTENT.

Now, bathing is commonly indulged in during the morning just at the hours of physiological collæmia, and when to this is added contraction of all the surface vessels by cold, and as we can now understand some increase of the urate precipitation itself by cold, it is little wonder that the heart is sometimes overpowered, and that powerful contraction of arterioles may bring the heart to a dead stop is acknowledged by Sir W. H. Broadbent ("Pulse," p. 153).

As regards my own pulse, I look upon a fluttering, imperfect systole or a dropped beat, as in fig. 36, as conclusive evidence of high tension. I have many hundreds of tracings of my own pulse, but none show these conditions without accompanying (causative) high tension, and I have often produced this condition or removed it in myself and others.

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With reference to some of the points just mentioned it is interesting to notice that Marey says that the pulse in typhoid fever is, first of all, soft and dicrotic, and later on the approach of convalescence shows more or less high tension, and he goes on, "L'apparition du triple rebondissement (= w pulse of high tension as in trace A, fig. 36) est un caractère important de l'approche de la convalescence; nous le rencontrerons a la fin des autres maladies febriles. Au moment de la convalescence le pouls présente parfois aussi un peu d'irregularité" (prev. ref. p. 569). That is to say, during high fever there is retention of uric acid, and little or none in the blood, but as the temperature begins to fall the alkalinity of the blood increases, it soon dissolves a considerable quantity of uric acid which produces high blood pressure, and the heart often flutters or falters as the pressure rises.

Dr. Chapman, in his interesting lectures on the "Physics of the Circulation," says that when the heart gives a tumble or flutter it really makes two contractions, as an effort at compensation (*Lancet*, 1894, vol. i., p. 661).

Again, with regard to alcohol, Marey says, "Certains agents l'alcool, par example, mettent la circulation dans un état analogue à celui de la fièvre typhoide; le pouls de l'ivresse à moins qu'elle ne soit accompagnée de troubles gastriques présente à un haut degré le dicrotisme" (prev. ref., p. 569). Why this exception in the case of gastric troubles? Marey appears from the context to attribute it to irritation of the abdominal sympathetic, but I am only following his own rule with regard to heart rhythm, just quoted, in suggesting that the absence of dicrotism in gastric trouble is really due to uric acid, and the intra-vascular pressure changes it produces, and not directly to the nervous system; for gastric upset means that there is diminished absorption of alcohol, or the acids so frequently ingested along with it, diminished absorption also of food with its resulting diminished formation of urea and acids, and the result of all this is an increase in the alkalinity of the blood, which at once takes up an increased quantity of uric acid, and this obstructs the vessels and prevents more or less completely the dicrotism which would otherwise be produced by alcohol and acids.

Marey also says that vomiting brings on coldness of surface and extremities, and that this is a very constant result, as everyone who is seized with nausea grows suddenly pale, has cold hands and a slow feeble pulse, in fact, all the signs of vascular contraction; he says also that John Hunter was struck with the coincidence of lowered temperature with vomiting, and drew from it the conclusion

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that the stomach was probably the seat of heat formation for the body. Marey proceeds to correct Hunter by referring to what is now known about the abdominal sympathetic and its supposed power of contracting the vessels all over the body, but he is probably himself quite as far from the truth as Hunter was.

The real explanation is, I believe, that in all gastro-intestinal disturbance, whether culminating in vomiting or not, there is a diminished formation of urea and acids (and one has only to watch the effects of dyspepsia on the excretion of urea for a few days to be quite sure about this), and consequently an increase in the alkalinity of the blood; as a result it is flooded with uric acid which produces deficient circulation throughout the body, and especially as we have seen in the skin. We now know that even in physiological conditions the temperature of the body is largely dependent on the quantity of uric acid in the blood (fig. 5), but from the vasomotor or abdominal sympathetic point of view it would have to be shown that these centres were more active in the contraction of vesels in the a.m. hours of each day than in the p.m. hours.

Some deficient circulation or vascular obstruction is the central symptom of every migraine in which the initial lesion is almost always some gastro-intestinal disturbance, though this is sometimes itself secondary to collæmia produced in other ways, as in fatigue (see chapter viii.), but once the gastro-intestinal disturbance is present it affects the alkalinity of the blood and produces or intensifies the collæmia to which everything else is secondary.

If the deficient circulation throughout the body in migraine is due to the abdominal sympathetic, why does clearing the blood and urine of uric acid control it? Why does increasing the uric acid in the body and blood make it worse?

It is, no doubt, delightfully easy to refer every ill-understood phenomenon to the irresponsible action of the abdominal sympathetic or the vasomotor centre, but no shadow of a reason is given us why these centres should fly into a passion and contract all the arterioles in the body simply because the stomach has had a slight disagreement with a pork chop. Migraine itself was said to be a neurosis till I showed that the nerve centres might be neglected if the uric acid was controlled, and the obstruction of vessels in this and all similar conditions is not nearly so sudden as Marey seems to suppose, for long before the stomach trouble is so bad as to produce vomiting, there has been more or less complete suspension of digestion and absorption, and during the whole of this time the alkalinity of the blood and the consequent collæmia have been

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increasing. Marey sees the final stage of the process, and looks upon the obstruction of vessels as sudden, but in migraine there is often very great obstruction of vessels without any vomiting at all.

One cannot help thinking what a sorry plight these nerve-centre theories would be in if the action of uric acid on the circulation should prove after all to be mechanical.

I do not deny that irritation of a sensory nerve may cause temporary contraction of vessels and a rise of blood pressure, but this may be due to contraction of the relatively large vessels, and is generally a very temporary matter, and differs in many ways from the steady and continuous high blood pressure which accompanies an excess of uric acid in the blood.

In migraine again, where the pressure remains high for hours, or possibly for one or two days, the only pain is in the head, and though there may be occasionally a little nausea there is certainly no abdominal pain sufficient to account for irritation of the sympathetic.

Then again in physiological conditions what possible source of vasomotor irritation is there in the a.m. and early p.m. hours which is absent in the later p.m. hours, or why does a dose of calomel affect the blood pressure at any time?

Still more in pathology as in chronic Bright's disease, when the blood pressure is high for days, weeks, months and years, does its remarkable relationship to uric acid come out; clear the blood of uric acid by means of mercury or watch it being cleared by an intercurrent febrile disturbance, and the high pressure vanishes in a comparatively few minutes and remains absent till the mercury or fever are gone, but no longer.

In these physiological conditions we are quite certain that the high pressure is not due to the contraction of the larger arteries, because the arteriometer tells us that the diameter of the radial increases with the pressure, and though these large vessels are no doubt exercising some pressure on the blood within them, this is with the object of helping the heart and forcing the circulation through the obstruction in front; it is quite obvious that as the large vessels are dilated the rising pressure cannot be due to their action.

If we apply this to all the arteries that have obvious muscular tissue, and consider that they are aiding the heart by a certain amount of contraction to force the blood through the obstruction in front; and that they with the heart become hypertrophied in the process and obviously the small vessels (arterioles) which are nearest

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to that obstruction, will have most pressure to bear, and may become most hypertrophied as a result, just as the small pipe near a tap is subjected to the greatest strain when the stream is suddenly stopped.

From this point of view, then, we see one nerve centre engaged both in physiological and pathological conditions in aiding the heart and arteries in forcing blood forward while another is engaged in contracting the capillaries and keeping it back, and that internecine warfare goes on between these centres for days, weeks, months and years, to the detriment of the physiology and nutrition of the body.

Is there any parallel to this condition of affairs in the rest of the physiology of the human body? Is there anything in the theory of evolution to make us believe that such a state of things is possible?

At this point my observation on the constant relationship of these conditions of high blood pressure both in physiology and pathology to excess of uric acid in the blood comes in, and we have to suppose that the uric acid irritates the second centre, and sets it against the first, for the moment uric acid is removed the strife ceases.

On the other hand, if it should eventually prove that the connection between uricacidæmia and high blood pressure is mechanical and due to blocking of capillaries by colloid uric acid, we are at once relieved from the necessity of believing in physiological suicide, and can see that the whole physiological resources of the body are really harmoniously working, united in one common endeavour to prevent this mechanical obstruction from doing injury to the nutrition and function of its tissues.

However this may turn out, one fact is, I believe certain, that both in physiology and pathology high blood pressure is absolutely dependent on the amount of uric acid in the blood, and that if we remove the uric acid we shall, on the one hand lower the blood pressure, and on the other improve the circulation through every organ and tissue of the body, and can do all this without the least regard to any nerve centre, however irritated or suicidally intent it may be.

Marey also points out that a feeble pulse becoming almost imperceptible in the radial, but presenting the pulse tracing of extremely high tension, is the pulse of *mal der mer*, and of nausea or vomiting. I would point out that in sea-sickness there is very commonly a headache, which has, I believe, all the characters of the ordinary bilious headache (migraine) produced by uric acid, and I see no reason to doubt that the high tension pulse is

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produced by uric acid, and that the headache represents the effects of the high blood pressure on the intra-cranial circulation, and a similar headache can be produced in anyone who, like myself, is prone to suffer from it, by anything which will produce gastric disturbance, provided he has a supply of urate in his body which can be taken up by his blood; and it is because I, thanks to a xanthin or uric acid free diet, have not this supply of urate that I now have immunity from headache.

On the other hand, where there is obstruction of capillaries, but the heart is powerful, perhaps hypertrophied, and refuses to give way, dilate or furnish imperfect systoles, tension will rise to a dangerous extent, and especially where the vessels are already degenerate, hæmorrhage will occur.

This may be comparatively harmless in the form of epistaxis or a more or less profuse hæmoptysis (and I have elsewhere[1] suggested that what the late Sir Andrew Clark has written about as "arthritic hæmoptysis" may be due to collæmia and its effects on the circulation) or may be fatal and deadly as hæmorrhage in the brain.

I am now collecting records of cases of syncope, hæmorrhage, &c., with the object of finding out whether a majority of them occur at the times of physiological collæmia, the "alkaline tides" of the morning or afternoon, pathological exaggerations of which may satisfactorily account for their causation.

As to the arteries themselves, high tension means a certain amount of strain, and strain is supposed to lead to degeneration of structure. Then it is at least probable that the vasa vasorum are among the vessels affected by the urate, and so nutrition is soon involved, and as effects of both causes we have degeneration, atheroma, and other changes. Hence in diabetes, a disease which is often associated with high blood pressure as pointed out in chapter xiv. we get arteriosclerosis, and gangrene associated with it (see *British Medical Journal*, Epitome, 1896, vol. ii., p. 17). The same argument applies to the heart. We get first hypertrophy and then degeneration, or we get sudden syncope or angina occurring in the alkaline tide, and due to obstruction of capillaries for which it is unprepared, the fluttering heart of uric acid headache or epilepsy being minor stages of the same thing. I shall have more to say about syncope and angina in chapters viii. and xiv., but its causation by the obstructed capillaries of collæmia follows directly from what I have said about fig. 36, and this explains completely its occurrence

[1] Wood's *Medical and Surgical Monographs*, February, 1890, p. 359.

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after fevers, influenza, &c., or in association with gout, dyspepsia, and glycosuria; it also explains the relief afforded by mercury, morphine and the nitrites, for all these drugs clear the blood of uric acid. Several of my epileptic patients have told me that they often shivered with cold (obstruction of the capillaries of the skin) or felt a fluttering in their throat (sign of a single non-habitual intermission of the heart) just before a fit comes on.

As to the skin, there is the cold skin of migraine passing through all stages of severity up to Raynaud's disease, or various interferences with function and nutrition, producing urticaria, erythema, &c., and where the skin has long been under the power of urates, perhaps leading to that atrophy and loss of structure described by Semmola (see chapter xiii.) as being present in Bright's disease.

With regard to Raynaud's disease again, one cannot but see that there is some difficulty in believing that a spasmodic contraction of living tissues should last so long as to produce death of the parts, and Raynaud has shown (see chapter xi.) that the obstruction is not in the arteries nor in the veins, but in the capillaries. But if the obstruction is due to colloid uric acid, we can see that the cooling of the blood in the exposed skin and extremities of the fingers may increase the precipitation of the colloid uric acid, just as it does in the test tube, and thus the local obstruction will not only be increased, but there will be no limit to its duration so long as the colloidal uric acid remains undissolved, and this possibly explains the remarkable way in which Raynaud's disease is limited to surfaces and extremities, and does not affect deep parts of large limbs, but such limitation is very difficult to explain by reference to an irritated nerve centre (see chapter xi., remarks on Dr. Southey's case).

In the brain we may have slow circulation or stasis as in headache, vertigo, epilepsy, and mental depression, and possibly œdema as in uræmia, all due to the effects of urates on its circulation, not to mention softening and hæmorrhage from organic arterial changes having similar origin.

In the cord we have, no doubt, similar functional and nutritional changes, and in the peripheral nerves, if I mistake not, neuritis and perineuritis, also due to vascular conditions produced by urates (see Charcot in *Prog. Med.*, vol. ii., 1890, p. 83-102, and Buzzard, *Lancet*, vol. ii., 1893, p. 1233), and toxic neuritis may represent the effects of the drug on urates. Then, again, there are many interesting eye symptoms which are more or less closely related to high arterial tension; for not only has

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stasis or thrombosis in the vessels of the retina been seen during attacks of migraine (see *Ophthalmic Review*, March, 1890, paper by Mr. Stanford Morton), but Dr. Lauder Brunton (*British Medical Journal*, 1892, vol. i., p. 7) and the late Dr. J. Anderson and others have noticed the connection between intra-ocular tension and high arterial tension.

It seems probable that in the eye we have a similar set of forces to those which bring about stasis and hyperæmia in the cranial circulation and that the pathology of glaucoma closely parallels that of headache or mental depression, and I have myself seen cases in which eye pain apparently related to glaucoma was immediately relieved by a drug which reduced blood pressure. Of the kidneys I have already said much, and of the way in which urates diminish the excretion of water and retain it in the body; one interesting effect of this is probably the œdema of eyelids, which has been noticed by several observers as occurring in migraine. I had my attention recently drawn to it by Dr. Gogarty, of Canterbury (see also *British Medical Journal*, 1888, vol. i., p. 1006, and compare anasarca case in chapter xiii.).

I have no doubt that the nutrition of the kidneys, liver, and other organs is eventually affected by the vascular changes which urates bring about in their parenchyma; the chief changes being an alternation of anæmia with hyperæmia, these being often intensified by the more serious secondary effects of the urates on the heart and general circulation.

The effects on the muscles can scarcely be less important than that on the skin and other organs, and when their vessels are obstructed by urates no doubt the nutrition of the muscles is more or less seriously interfered with (see the causation of fatigue, chapter viii.), and as they, like the liver, are important organs of metabolism, there can be little doubt that general nutritional changes may be seriously interfered with when their circulation is impeded: I shall have to suggest that in glycosuria, and albuminuria when temporary and not associated with actual kidney lesion, we may see results of such metabolic disturbance. Whenever blood pressure is high, and it is lowered by giving an acid, I have noticed that there is almost certain to be a rise of urea; I have suggested that this rise of urea is due to an increased formation of urea, when the metabolic processes in the liver, muscles, &c., are set free from the restraining influence of collæmia, and we shall see this to a much more marked extent in chapter viii., where it will appear that the amount of uric acid in the blood not only controls the amount of fatigue which a

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given exertion will produce; but also controls its effects on the formation and excretion of urea.

The late Dr. King Chambers appears to have regarded vascular tension as due to the presence of waste products in the blood, and treated the condition by diet; I may say that he took a great interest in the early stages of my research, and wrote me several letters containing points of great interest; among others he mentions a case of epilepsy, which rather to his surprise was apparently cured by diet. Dr. Chambers ordered his patient to reduce his meat and beer, but he being young and enthusiastic went beyond his instructions, and left off both entirely; eighteen years afterwards he had never had another fit; I shall have to relate a somewhat similar case in chapter vii. The step from the general belief that high blood pressure is due to waste products in the blood to the special belief that it is due to uric acid, is in some respects a small one; but I trust it will be seen that in the power it gives us to control high blood pressure and its effects, it is really a very large one.

It may be both interesting and useful at the end of this chapter to restate shortly in the form of conclusions some of the points and arguments that have been touched upon in the preceding pages with reference to the causation of high blood pressure by uric acid, thus:—

The daily, hourly, and seasonal variations in blood pressure are practically inexplicable if uric acid fluctuations do not cause them.

So are also the well-attested effects of milk diet or other uric acid free diets in lowering blood pressure, and as the condition of the blood and tissues is as good or better on these diets as on meat, it cannot be said that the lowering of blood pressure is due to any failure of nutrition on such diets.

There is a most interesting parallel between the known solubilities of colloid uric acid in glass and the action of acids, alkalies, and cold on the blood pressure.

Everything that clears the blood and urine of uric acid lowers blood pressure.

Everything which causes a plus excretion in the urine raises it, but the effect is proportional, not so much to the dose of the drug as to the amount of uric acid it has to act upon.

No other explanation of the action of metals, acids, lithia, etc., on the blood pressure has been given except their effects on the solubility and excretion of uric acid.

The effect of swallowing uric acid or its salts, or practically any

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xanthin compound, is first to lower blood pressure, and then as uric acid is passing in excess in the urine to raise it.

The reactions in the blood of the substance which raises blood pressure are those of uric acid, as every metal known to form an insoluble compound with uric acid clears it out of the blood, and consequently out of the urine; the mineral acids again do the same.

It has been suggested that the substance in the blood is para-xanthin, but para-xanthin forms a soluble compound with hydrochloric acid (see Chemical basis of the Animal Body, p. 178), while hydrochloric acid clears the blood of the substance we are looking for and lowers blood pressure, acting just like other things which form insoluble compounds with uric acid.

The solubilities of uric acid completely explain the production of bradycardia by disease and the action of drugs in relieving or preventing it.

The causation of many forms of syncope is also completely explained, and it can be shown that many of those who suffer cease to do so under otherwise exactly similar conditions, when their blood and urine are kept clear from excess of uric acid by means of diet.

The cause of many alterations in the rate of the heart's action is completely explained; as also the influence of drugs upon it, and the relation of hæmorrhage to high blood pressure and its cure by drugs.

On the other hand the supposed irresponsible action of the nervous system lands us in great confusion, and would force us to believe in the internecine warfare of nerve centres, and physiological suicide.

No other explanation has yet been given of the relation between the excretions of uric acid and of water in the urine.

No other satisfactory explanation has yet been given of the limitation of Raynaud's disease to surfaces and extremities.

Nor is it easy to believe that any muscular tissue can possibly remain contracted a sufficient length of time to cause its own death from gangrene.

While if the capillaries are mechanically obstructed by a storm of uric acid globules, these may not only remain indefinitely undissolved, but are certain to do so the more the circulation slackens and the temperature of the part falls, for cold precipitates uric acid.

Anything that clears uric acid out of the urine and at the same time lowers blood pressure may produce or precipitate an attack of

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gout in some fibrous tissue or joint, this showing where the uric acid has gone to from the blood, and why it fails to appear in the urine.

Where there is bradycardia, that is, where the heart does not complete more than sixty cycles in a minute, where the radial artery rolled under the points of three fingers feels full between the beats, and the arteriometer shows a more than usually large diameter, and the pulse gives a tracing as in fig. 37, where the first sound of the heart is long, and the second sound both at the apex and over the aortic area is loud, and where also the skin and extremities tend to get easily cold, and the urine and other secretions tend to be scanty: where the temperature in the mouth and rectum are far apart and are perhaps also, both of them, lower than in the corresponding hours of a normal day, there can be very little doubt about the presence of high blood pressure; and where it is present, and there is reason to believe that it is doing harm, the obvious indication is to reduce it.

Now every drug mentioned in chapters ii. and iii., as diminishing the excretion of uric acid in the urine will, when it does this, lower the blood pressure, quicken the pulse and free the circulation throughout the body. And what we have to consider here is which of these drugs will do this best and most certainly under the circumstances present in a given case.

Speaking generally, those things will act most certainly which, like the metals and their salts, form directly insoluble compounds with uric acid, and are independent of the rise and fall of the alkalinity of the blood.

For acids and substances which act by raising the acidity of the urine and lowering the alkalinity of the blood may obviously be overcome, or have their power reduced, by conditions such as fatigue, heat, and perspiration, vomiting, diarrhœa and gastro-intestinal disturbances in general, which tend to lower the acidity of the urine and raise the alkalinity of the blood.

So that where any of these conditions are present or likely to be present, I make use of one of the metals, generally mercury.

And the action even of mercury is to some extent dependent on its not purging and not causing gastro-intestinal irritation or diarrhœa; if it causes mercurialism with salivation and gastro-intestinal derangement, its power over uric acid will very quickly be reduced, and it will then cease to lower the blood pressure or quicken the pulse.

Generally speaking, I rely on the action of mercury, or that

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combination of it with iodine found in the ordinary mixture, containing liq. hydrarg. perchlor. ʒi., and iodide of potassium gr. v., when we get the retentive action of the iodine added on to that of the mercury (see figs. 17 and 21) with the utmost confidence.

The wonderful effects of mercury on the circulation are well seen in a most interesting and instructive case published in the *Lancet* (1895, vol. ii., p. 779), by Dr. Murray; here cardiac tonics and stimulants failed and were given up as useless, but mercury in the form of blue pill, which was taken to the extent of 20,000 grs., kept the patient alive for ten years, and during the whole time we are told that it neither purged nor salivated him, and we know that if it had done either of these it would not have acted on the circulation nearly so well as it did.

If they fail owing to gastro-intestinal disturbance, the only thing to do is to treat the gastro-intestinal condition with bismuth, opium and similar drugs, for probably nothing will affect the uric acid till this has been done, though a subcutaneous injection of morphine may be tried.

When we have to treat slight conditions of high blood pressure, and when physiology in general is but little disturbed, a simple acid mixture will suffice, as nitro-hydrochloric acid with perhaps the addition of a little strychnine.

If we want to act very quickly the nitrites are the best things, or a small injection of morphine, and their action may be continued by the use of ammonium, or the iodides of sodium or potassium or of wine, ether, and similar stimulants.

If we want to act steadily over a long period of time the iodides are the most useful, or the iodide of mercury if it does not upset physiology, in this case try other metals, as zinc or copper.

All these drugs clear the blood of uric acid and lower the blood pressure, and free the interstitial circulation as a result of this; but they clear it out of the blood into the tissues, and do not eliminate it from the body, and it is necessary to bear this in mind, for when they are left off the uric acid thus held back will tend to get into the blood again, and the last state of the patient may be worse than the first.

But this difficulty can be overcome by giving a course of salicylates for five to ten days, either with the last doses of the retentive drug, or immediately after it has been left off, this will carry off the stores of uric acid and prevent them doing any harm.

I may mention also that when mercury is contra-indicated we have a valuable means of lowering the blood pressure in a course of

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acids and salicylates given concurrently—the acid mixture before meals and the salicylate after.

The acid prevents the uric acid from combining with neutral phosphates or alkalies in the blood (these being the compounds which appear specially to affect the blood pressure while the compound of salicylic acid with glycocoll hardly, I think, affects it at all), while the salicylate holds it in solution and passes it out of the body; so that this treatment has the advantage of being followed by no rebound.

Diet, of course, by reducing both the introduction and formation of uric acid offers the most permanent and satisfactory means of lowering blood pressure, and of this I shall speak in chapter xvii. My alteration of diet has not only removed my migraine, but has freed my circulation and reduced the general level of my blood pressure, and so delayed or prevented Bright's disease and other troubles of nutrition, due to impeded and defective circulation in the tissues.

Now let us use our knowledge to treat for instance a case of hæmorrhage; we must enquire first of all whether it comes from the arteries or from the capillaries and veins, whether it comes from the distal or proximal side of our screw clamp in the imitation circulation previously mentioned. If from the capillaries on the distal side of the clamp the obvious indication is to screw up the clamp, and this is, I think, the way in which ergot stops such hæmorrhage as that from the uterus, though even here high blood pressure has some influence in increasing the flow of blood. On the other hand, when the hæmorrhage is arterial, as from an eroded vessel in the stomach or the lungs, or a ruptured vessel in the brain, the indication is to lower blood pressure by relaxing the screw clamp as much as possible; and this is, I believe, the way in which such drugs as opium and lead relieve, as their first action is to clear the blood of uric acid and lower the blood pressure; and we must beware that their second action or rebound (see fig. 34) does not occur too soon, *i.e.*, before the vessel is securely plugged, or we shall have a return of the hæmorrhage.

If arteries the size of the radial dilate with every rise of blood pressure as the arteriometer shows, the great importance of reducing blood pressure in arterial hæmorrhage must be obvious, and these considerations led me to use the iodide of mercury mixture in the treatment of hæmoptysis, with results which have often seemed to me to be very satisfactory. It acts, as will now be understood, in exactly the same way as lead, opium, and other things more commonly used.

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And my friend, Mr. J. E. Frazer, formerly House Physician at the Metropolitan Hospital, and now one of the Residents at the Royal National Hospital, Ventnor, tells me that he has often seen it used with benefit, especially in hæmoptysis, coming in the morning hours and associated with headache (? hæmoptysis due to collæmia). I often found, however, that the hæmoptysis returned when I left off the mercury and iodide, till I took to following it by salicylates. I have also been much interested to see that Prof. Mays (*New York Med. Journ.*, 1896, 27th June), has been led by my statements to use salicylates with success in a case of phthisis, with pains in the chest and arms, and also in some kinds of hæmoptysis (see also *Philadelphia Polyclinic*, vol. 5, Oct. 1896).

It may be of some interest, in relation to the treatment of hæmorrhage, to remember that Mr. J. Hutchinson has pointed out, in his "Archives of Surgery," that a very reliable method of curing epistaxis is to plunge the hands and feet in very hot water, for such treatment would promptly put a stop to local collæmia, and by returning warm in place of cool blood to the deeper parts would no doubt soon revive the temperature of the whole mass of the blood, and thus clear up collæmia in general, and lower the blood pressure, acting in much the same way as the iodide of mercury or the draught of urine previously spoken of, and we shall see that similar treatment of hands and feet is a valuable measure in the uric acid headache, no doubt also from the effects on collæmia and blood pressure.

I have certainly several times seen epistaxis come on during exposure to cold, and it seems very probable that the running of water from the nose, which is a very frequent effect of cold in many people, is but a minor condition of the same thing, and represents the physiological result of the collæmic obstruction of vessels and high blood pressure which cold produces, and carry this but a step further the congestion of the vascular mucous membranes of the nose is so great as to cause hæmorrhage; apart from any marked action of cold, such hæmorrhage is in my experience most common in the a.m. hours, when there is for other reasons most collæmia.

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CHAPTER VI.

Headache.

The headache which I have ventured to call "the Uric Acid Headache" from the result of my investigations as to its causation, is, I believe, the same thing as migraine, megrim, sick or bilious headache, for an account of the history, symptoms, and relationships of which to other diseases, we owe so much to Dr. Liveing.

And, as before mentioned, it was his most interesting work which turned my attention to the urine as a possible source of information as to the gouty relationships, and so as to the causation of the headache.

The points about this headache which, to my mind, best serve to distinguish it from others are (1) its periodicity; it occurs once in a week, fortnight, month or longer period, for many years, or for the whole life of a patient; it tends to be more frequent and severe in the spring and early summer (see fig. 4), and in women it almost always attends the menstrual epoch (see figs. 30 and 31); when present it tends to be worst at those hours of the day in which the excretion of uric acid is normally greatest (see figs. 2 and 3). (2) Its duration is generally under twenty-four hours, though in exceptional cases it may last for forty-eight hours: a patient goes to bed with a more or less severe headache, and wakes in the morning free from it. This short duration is of great diagnostic importance in distinguishing it from the more continuous headaches such as those due to neuralgia or intracranial disease, which often last for days or weeks with little or no alteration. The uric acid headache is due to the passage of an excess of uric acid through the blood; but apart from organic disease this (uricacidæmia) can for obvious reasons only last a few hours, the uric acid is all excreted, and the headache will pass away with it.

The eye symptoms of this headache which have also been carefully described by Liveing have only affected me occasionally, but

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have been more marked of late years, when the headaches have been both less frequent and less severe than they were 10—12 years ago.

Their most frequent form in myself is that of finding half an object blurred as the upper or lower half of a picture or the right or left hand side of a page, I have also very frequently had flickering as of a fortification pattern, or like the flashing of light on quickly rippling water, and this more often at the right of the field of vision than elsewhere. On the other hand, both my children suffer or did suffer from this headache till cured by diet, and in them the eye symptoms have been the rule rather than the exception, so that they themselves distinguished febrile headaches such as that of influenza by the absence of the eye symptoms.

As noted by Liveing and others the pulse is slow and of high tension (see fig. 37), the surface and extremities are cold, and the

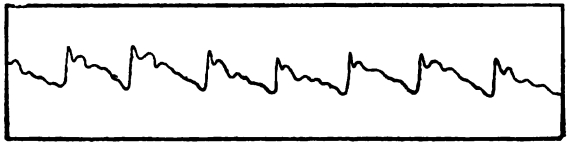

FIG. 37.—PULSE TRACING OF HIGH BLOOD PRESSURE IN A URIC ACID HEADACHE.

temperature even in the axilla is subnormal. (Some observers have noted pulses of 48 and 52 during the attack. See Fagge's "Medicine," Ed. 2, vol. i., p. 784).

The tongue may be clean or slightly furred, the appetite may be fair but is often irregular, a feeling of emptiness and ravenous hunger being quickly replaced by a feeling of distension and satiety: in fact there are signs of dyspepsia, though they are often slight. When the headache is severe there may be nausea or vomiting; but these are generally late symptoms, and are absent or little marked when the headache first comes on.

The bowels may be regular and the motions natural; but, commonly, like the appetite, they are a little irregular, either slightly relaxed or slightly constipated.

The urine during the attack is scanty and of high colour and sp. grav.; thus in the attack it may not exceed 30—40 c.c. in the hour; after the attack, and especially just as it passes off, it may run up to 100 or 150 c.c.—or more—in the same period.

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There is often a family history of headache of the same type, or of epilepsy together with gout and rheumatism, and not very rarely phthisis; chronic nephritis and cerebral hæmorrhage should also, I think, be added to the list of family complaints.

When a headache has a majority of these characteristics well marked there is rarely much difficulty as to the diagnosis; but there are several important ways in which we can put our diagnosis to the test.

If the scanty urine of the headache is carefully separated from that passed before and after, it will be found to contain a relative

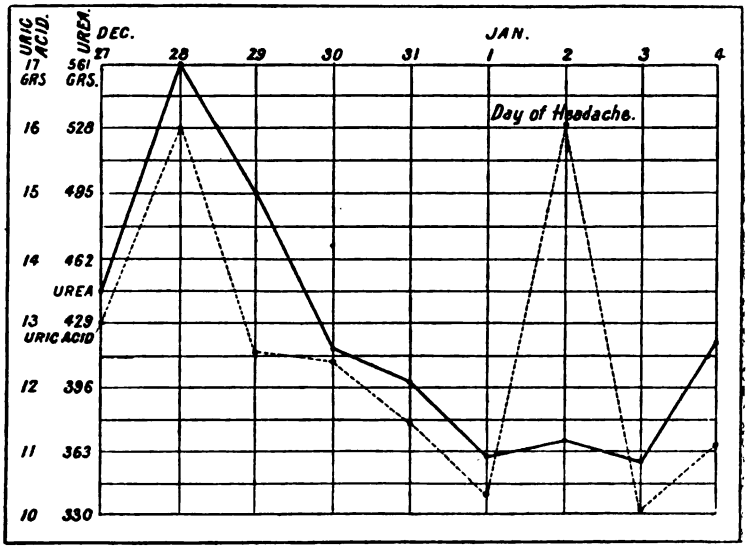

FIG. 38.—CURVES SHOWING THE EXCRETION OF URIC ACID BEFORE, DURING, AND AFTER A HEADACHE.

excess of uric acid having a relation to urea varying in different cases from 1—25 to as much as 1—12 or 1—15, and, generally speaking, the greater the relative excess of uric acid and the greater its absolute excretion per hour, the more severe the headache; thus with a headache I find ·6 gr. of uric acid per hour and upwards, and when I have removed the headache by acids the excretion falls to ·45 gr. per hour or less; the urinary water undergoing, as before mentioned, an inverse change. Fig. 38 shows the excretion of uric acid and urea on nine consecutive days, on one of which there was a

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severe headache lasting nearly the whole twenty-four hours. The way in which the uric acid runs up apart from urea is well shown, and it is also seen that the uric acid was below the urea on each of the six days preceding the headache; and if we add together the amounts by which uric acid fell short of urea on these days it shows that there was a total retention of about 4½ grs., and this is almost exactly the amount by which uric acid exceeded urea on the day of headache. Then again, from December 28 to January 1, urea fell steadily, and with this fall no doubt acidity would fall also to a corresponding extent, and the result of this sooner or later was sure to be a plus excretion of urate and a headache.

This figure also well illustrates what occurs after several good dinners or any other causes that run up the introduction as well as the formation of uric acid and urea. As the urea and acidity go up the patient feels very well and thinks he is all the better for them, because uric acid is being retained; but as urea and acidity fall, as they are bound to do later on, the stored uric acid is bound to come out, and then he will have headache, mental depression, or other disorder as the result of his indiscretion (see fig. 24, and *Journal of Physiology*, vol. xv., plate x., fig. 4).

All so-called biliousness is practically uricacidæmia, for though anything that upsets digestion (as irritating or indigestible food, cold, &c.), will cause uricacidæmia as its result; excess of uric acid in the blood from previous excessive introduction followed by a natural fall in acidity will suffice to upset the circulation in the liver, stomach and intestines and so to produce dyspepsia and biliousness.

It is evident, therefore, that we can not only explain every feature in the causation of this headache, but can imitate nature, control uric acid and urea, and produce the disorder at pleasure.

This was the trouble which originated my research, its relationship to gout and its subsequently discovered relationship to meat diet serving to direct my investigations. Both these relationships can now be completely explained, that to gout and rheumatism being simply due to their common connection with the quantity of uric acid in the body and blood, and that to animal food depending on the fact that all animal substances, extracts and infusions from the tissues of animals, &c., contain, and consequently introduce into the body, a considerable quantity of uric acid or of xanthin compounds, equivalent to it (see figs. 24 to 29). We now know that if such animal tissues and extracts are left off while such vegetable alkaloids as are equivalent to uric acid, as theine and caffeine, are as far as possible avoided, the uric acid headache (migraine) with all its con-

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comitant symptoms vanishes from the life history of the individual who thus changes his diet, and this similarly includes the cure of nearly all the diseases treated of in this book, so long as they are functional and have not become organic and beyond all cure.

This knowledge also gives us power to cure the headache when present or to produce it at pleasure in those who, owing to the size of the arteries which supply the brain, are anatomically and physiologically susceptible. The headache is thus seen to be due to poisoning by flesh food, and tea, and to be most frequently met with and obvious in those who, having large arteries of supply to their brain, are most affected by the high blood pressure which uric acid produces. There is absolutely no anatomical or physiological defect in the individuals who thus suffer, on the contrary they are, as has frequently been remarked by others, often intellectually superior to those who do not suffer.

In illustration of some of these points I will now explain the way in which a slight or severe headache may be brought about intentionally or otherwise.

And first let us have an intentional headache: our problem is to produce a fluctuation in the excretion of uric acid so that 4 or 5 grs. shall be prevented from passing out in the natural way, shall be retained in some part of the body, be dissolved out and again enter the blood a few hours later, and in passing through it produce headache and other symptoms.

As above mentioned, the largest excretion of uric acid in the twenty-four hours takes place in the alkaline tide of the morning, and one of the simplest ways of producing a fluctuation in excretion is to interfere with the natural plus excretion of the alkaline tide (see figs. 2 and 3).

By giving any of the drugs in the list of those which diminish the excretion of uric acid such as acids, opium, antipyrin, mercury, either before, with, or soon after breakfast, a certain amount of uric acid will be held back from excretion during the morning; but if no more of the drug is given the acidity will fall, either some time in the afternoon, or in the morning of the next day, and then the uric acid kept back in the morning will be taken up in the blood and begin to pass out by the kidney, and more or less headache and other symptoms will result.

Another very simple way is to take a little opium with or after lunch; this will raise acidity and interfere with the uric acid excretion of the early afternoon, and hold back some uric acid; then next day there is sure to be some plus excretion of uric acid with slow

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high tension pulse, headache, &c., in the early alkaline tide of the morning (fig. 34).

It must clearly be understood that I am here speaking of physiological conditions, and of the action of drugs on uric acid in persons who are in perfect health; where there is functional disturbance, and still more when there is organic disease, the conditions are much more complex (see chapter 5).

Suppose only that a patient has dyspepsia and fails to absorb his food, acidity and urea both get less and less, and a lowered acidity of the urine may continue the whole day and a plus excretion of uric acid will result for the same period, or till, as the gastric conditions improve, food is again absorbed, the urea and acidity curves rise and the excessive excretion of uric acid is put an end to.

And these considerations explain what is seen every day as to the effects of diet in preventing or producing a uric acid headache; if, say, a patient has a slight headache but is still able to take food well, a good dinner with a liberal allowance of wine may remove his headache and make him feel much better because it (especially the wine, see fig. 54) raises the acidity and clears the blood of uric acid; and this rise of acidity will commonly continue next morning, and he will feel bright and well next day also; but if he eats and drinks at this dinner not wisely but too well—if he takes so much both of food and of wine as to overpower gastric digestion—the effect will be very different, digestion will cease, and be replaced by nausea and vomiting, and with this urea and acidity will fall and the uric acid will soon be again in excess in the blood, and a severe headache will occur next morning in place of the well-being and brightness, which would have been present if the stomach had not been upset: the second day after a dinner, however, urea and acidity will fall, and then the headache will return unless the uric acid be in the meantime removed by a few doses of a salicylate, which is the way in which I commonly ward off the evil effects of a dinner.

Again, suppose that we have organic disease of the stomach, such as ulcer or new growth, the fall of urea and acidity will be constant and progressive. Suppose that urea falls from 500 grs. to-day gradually to 400, 300, and even 250 grs. in twenty-four hours, the acidity in its relation 1—6 would suffer a corresponding diminution, and the excretion of uric acid would be constantly large, and this state of things would go on till all the stores of uric acid in the body were exhausted, or till something occurred to raise the acidity.

Hence it comes about that a patient slowly dying of wasting

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disease will excrete for weeks and months an excess of uric acid, and if the urine is examined, uric acid will be found constantly above its normal relation to urea—1—35 or 1—40, and this will continue so long as the patient has any uric acid in his body which can be got into solution.

Hence it comes about that in patients who die after weeks and months of wasting disease we find only erosion of joint cartilages but no urates; we should have found the urates in the urine if we had looked for them at any time in the last six weeks, or attention may be called to the excessive excretion by the occurrence of gravel or calculus, but if the same patient had been killed six months ago by acute disease (as pneumonia) we should probably have found them *in situ*, all the erosions being filled and plastered with urate, because during the high acidity of the acute fever there had been no alkali to wash them out. Sir A. Garrod records ("Gout and Rheumatic Gout," ed. iii., p. 467) an intimate relationship between gout and stone, the one alternating with the other, and this, from my point of view, is most simple and easy to explain, for the self same uric acid which causes gout of the fibrous tissues or joints when passing out of the body through the kidney causes gravel or stone; when the alkalinity of the blood is low it is driven out of the blood into the joints, causing gout; when the alkalinity of the blood is high it is taken up from the joints and fibrous tissues, and passing through the kidney causes gravel, hence these two conditions alternate, what is good for the one being bad for the other.

We can now see that those who speak of erosion of joints without urate deposit as "rheumatoid," and the same erosion with urates as "gout," are endeavouring to make two diseases out of different stages of the same process.

But to return to the causation of headache. If a patient has chronic wasting disease none of the drugs in our list will be able to stop the plus excretion of uric acid: acids, opium, antipyrin—all will alike be overpowered by the flood of alkali; or where the disease is only functional our drugs may still fail to effect a cure, either because the functions of the stomach are too much upset to permit of their being absorbed, or because, after more or less absorption has gone on the acids are over-powered by the action of the causes that increase alkalinity. In the case of opium, which, I believe, raises acidity by acting on the intestines, delaying peristalsis and increasing absorption, it is obvious that extensive ulceration may produce so much diarrhœa that only a very large dose of the drug will have any effect.

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Under these or similar conditions almost any drug in our list, or several combined, will fail to check the plus excretion of uric acid, or to remove the symptoms which are due to its excess in the blood.

In the above cases of very chronic plus excretion of uric acid the excess is not generally very great, and though the presence of some excess of uric acid in the blood is constant, the quantity may not be enough to produce a distinct headache, except now and then for a few hours; but the patient suffers continually from some minor signs of collæmia, of which we shall speak presently.

But speaking generally, and bearing in mind the above causes of failure, a uric acid headache, accompanied by a plus excretion of uric acid, can be cured within an hour or an hour and a-half by anything that will raise the acidity of the urine or otherwise stop the plus excretion of uric acid, and if in any given case we fail to cure the headache we shall find, if we examine it, that we have also failed to raise the acidity of the urine, or stop the plus excretion of uric acid.

We can now explain all the main symptoms and characters of this headache, and first its periodicity: being as I have said, due to a fluctuation in the excretion of uric acid, the first stage of the fluctuation is a holding back or retention of urate in the body, and during this process there will be little or no urate in the blood, and no headache; on the contrary, the signs will be those of absence of uric acid from the blood, just such as are produced in the first stage action of opium, mercury, cocaine, lead, zinc, acids, &c. The patient will feel more than usually bright, happy, cheerful and energetic, and there will be no sign whatever of headache; and it depends upon the length of time occupied by this process of retention how long an interval will be interposed between successive headaches.

On my old meat (ordinary) diet I used to have a headache once in seven to ten days, that is to say, in five to seven days I had accumulated sufficient uric acid to produce another excessive excretion; on my present diet, I not only form and introduce much less uric acid, but as acidity is no longer raised by the acids and acid salts of animal food, but rather kept down by the alkaline salts of fruits and vegetables, nearly all the uric acid I form and introduce is at once excreted, and only very occasionally, and at long intervals, or after some excess in nitrogenous food, do I accumulate enough in my body to produce a headache as it passes through the blood.

But the fact that I do thus occasionally get a headache shows that there has been no anatomical or physiological change in my

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body and that we have only to introduce enough uric acid into the blood to bring it back again.

The onset of a headache is often preceded by a period of more than usual mental brilliancy and well being, this corresponding with the fluctuation of uric acid excretion which precedes the attack in nature, just as it does when an attack of headache is produced in one of the ways above mentioned. Exactly the same thing has been noticed to occur before the fit of epilepsy, and as we shall see, it is probably due to the same cause.

The relation of headache to menstruation in females is also easily explained, for menstruation is almost always a cause of some little general disturbance of function which often specially affects the digestive organs, so that food is taken badly or badly digested, and exercise is generally deficient. Several of these causes combined bring about some failure of nutrition with a fall of urea and a corresponding fall of acidity, and this is the signal for any uric acid that is on store to be got into solution and flood the blood, hence menstruation is commonly accompanied by a lowered acidity, a plus excretion of uric acid, and the effects of its excess in the blood, such as the slow high tension pulse noted by Sir W. H. Broadbent, and mental depression, of which I shall speak later; and if there is much uric acid on store, more or less severe headache or an epileptic fit (see figs. 30 and 31).

The reasons why the headache is worst at the hours of normal plus excretion of uric acid—that is, in the periods of low acidity after breakfast and lunch—are now, I hope, too obvious to need further mention. As a rule, and when the kidneys are normal, the five or six grains of uric acid which occasion a headache by their passage through the blood are all excreted in a few hours, and the headache subsides, this explaining its usual short duration. But I have seen several cases in which the attacks of migraine which had been in attendance for years, had suddenly become more frequent, severe and prolonged, and in these cases further investigation has proved that Bright's disease had supervened, and that an organic cause of uric acid retention had been added to the original functional one (see chapter xiii.).

As regards the causation of the headache, the effect which, we have seen, that uric acid exerts on all the vessels of the body is closely allied to that which, occurring locally, has been supposed to be the cause of the pain. Thus it has been suggested by Du Bois Reymond and others, quoted by Liveing (p. 295 *et seq.*), that the headache is due to irritation of the vasomotor nerves in the region

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of the cervical sympathetic giving rise to contraction of vessels in certain areas, followed by dilatation and congestion, which produces pain. Again, Dr. Brunton (*St. Bartholomew's Hospital Reports*, vol. xix., p. 333) has suggested that the proximal ends of certain vessels are dilated, while the distal ends are contracted, and that the impact of the blood against the contracted extremity produces pain. I think, however, that the effects of uric acid in obstructing the peripheral vessels and producing high blood pressure and the further effects of this high blood pressure on the intra-cranial circulation, will give us a much better explanation of the causation of the headache than any more or less hypothetical irritation of the cervical sympathetic.

Taking it for granted, then, after what has been said that an excess of uric acid in the blood does obstruct the capillaries, and cause high blood pressure, the researches of Professor Grashey, which I have quoted at length in *Brain*, Spring and Summer Number, 1893, show that when arterial tension rises above a certain point, the pressure in the closed cavity of the skull becomes so great that the veins are compressed and begin to vibrate, the blood stream through them being greatly hindered, and from this results more or less stasis and hyperæmia in the veins and capillaries behind the point of compression, with general excess of pressure in the cranial cavity.

But the process does not stop here, for Professor Grashey further suggests that as the cerebro-spinal fluid comes from the blood, the above condition of stasis and hyperæmia may bring about an increase in its quantity, and so still further increase the intra-cranial pressure.

It appears to me that such a general increase of pressure acting within the unyielding membranes of the brain may account for the pain of headache, in so far as it is bilateral, and that where it is unilateral, or apparently affecting chiefly the distribution of a single nerve, there may be some œdema affecting specially the sheath of that nerve, and due to the changes in the circulation, just as the more general increase of cerebro-spinal fluid may be due to it. And we may probably account in the same way for the paralysis or paresis of certain nerves which sometimes occurs contemporaneously with a migraine (see *Lancet*, 1893, vol. ii., p. 139), and stasis or thrombosis which would probably produce œdema and pressure have been actually observed taking place in the vessels of the retina during an attack of megrim. (See article by Mr. Stanford Morton, *Ophthalmic Review*, March, 1890.)

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As regards the bilateral headache, I have to thank Dr. W. Rushton Parker, of Kendal, for reminding me of the interesting fact that Mr. Victor Horsley has pointed out *(British Medical Journal*, 1893, vol. ii., p. 1366) that opening the skull invariably cures the headache of cerebral tumour by relieving the pressure, so that the similar intense headaches of migraine and cerebral tumour may both be due to excessive intra-cranial pressure.

A rise of blood pressure means, as we have seen, an obstruction of capillaries throughout the body, and a deficient circulation in all the tissues; and the brain tissues probably share this deficient circulation, and such minor effects of function as are expressed by mental depression and increase of irritability may be its clinical signs; but if the block in the capillaries becomes still greater, and the pressure rises still higher, we get an effect on the intra-cranial circulation which differs from that on the rest of the body.

The pressure acting in a closed cavity compresses the veins at their point of entry into the large sinuses, and we get more or less venous hyperæmia and stasis, and, after this has lasted some time, increase of cerebro-spinal fluid, and so still further increase of intra-cranial pressure. The effects thus produced are much more serious and pass beyond the region of physiology into that of pathology, and have such symptoms as headache, vertigo, or the fits of epilepsy or uræmia as their results. So absolutely constant are these results that with many people it is possible to form a fairly accurate estimate of their blood pressure simply from their temper; when this is short, blood pressure is high, when it is calm and placid, blood pressure will be distinctly lower.

With regard to the causation of the uric acid headache, I have noticed in my own case a fact of some interest, namely, that when the pain is severe and situated, as is often the case in my attacks, in the centre of the occiput (? neuchalalgia of Dr. Burnett, see chapter viii.), sitting with the head bent back so that the face looks vertically upwards will greatly mitigate the throbbing pain, and it has occurred to me that this position may in some way interfere with the increased pressure of arterial blood that corresponds to each throb. Speaking generally, the vertical position is the only one which is bearable in migraine; when I have an attack I am obliged to sit vertically upright against the back of my bed and slide gradually down into the usual recumbent position as the pain moderates; then again, stooping makes even a slight headache unbearably severe, and the effects of position on intra-arterial pressure suffice to explain these facts, for Marey says: "Dans l'attitude

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verticale un animal aura donc une pression manometrique plus faible à la carotide que la femorale et surtout que la métatarsienne." ("La Circulation du Sang," p. 192.)

In the vertical position gravity is acting against the circulation in the carotid, with it in the femoral, and both the sphygmograph and the arteriometer show similar changes of pressure and diameter in the radial artery, when the arm is raised, horizontal, or hanging down.

The fact that compression of the carotid has often been used to relieve the pain of the headache tells in the same direction (see Dr. Liveing, "Megrim and Sick Headache," pp. 376-7).

Exercise again affects the head pain in accordance with its effect on intra-arterial pressure; thus the first effect of muscular exertion is to raise blood pressure and make the headache worse: but if the exercise is persevered in to the extent of producing general relaxation of the vessels in the muscles, with warm and perspiring skin, this general dilatation of vessels brings about a fall of blood pressure, and the headache departs, and the patient is again able to take a cheerful view of things.

And though part of the fall of blood pressure is, no doubt, due to the increased area of circulation in the muscles, we must not forget that the increased production of heat will tend to clear up the collæmia and so free the capillary circulation of the whole body, and still further lower the blood pressure.

Vertigo is one of the most interesting of the occasional results of high tension, and as its causation is probably exactly parallel to that of headache and epilepsy, it throws an important side light on their origin.

Murchison classed vertigo among the disorders associated with lithæmia, and Dr. Buzzard ("On Vertigo of Bulbar Origin," *Lancet*, 1890, vol. i., p. 179) points out that a gouty history is very common, and that salicylate of soda is useful in treatment, a fact which he explains by reference to my researches on the action of this drug on uric acid.

In so far as vertigo is of "bulbar origin," I take it that it is the exact parallel of uric acid headache or of epilepsy, and that the high blood pressure and consequent increased intra-cranial pressure which produces the latter, may produce also the former trouble; and, indeed, I have had several cases of vertigo in patients with high arterial tension in which the reduction of tension has effected great improvement or cure of the disorder.

It is evident, then, that all that has been said about the causa-

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tion of headache or that remains to be said about its treatment will apply also to vertigo.

Dr. Buzzard (previous reference) mentions that these attacks may be followed by a large discharge of colourless urine. Here again we have an exact parallel with epilepsy and migraine, and the causation of the symptom I have previously gone into.

I have myself had one or two attacks of temporary vertigo, and these came in the morning at a time when blood pressure is generally high and the uric acid in temporary excess in the blood, and I looked upon it as a variation of my migraine with which, as regards time of onset and attendant symptoms, it corresponded.

Dr. Buzzard suggests that this vertigo may be due to an effection of the bulb near the origin of the auditory nerve, and signs are not wanting, along with the headache, mental depression, and other symptoms of uricacidæmia, of some slight functional derangement in this region, for I have several times pointed out (*Brain*, 1891, and elsewhere) that with these signs of uricacidæmia a certain amount of aphasia with forgetfulness of names, &c., is very commonly associated, and Dr. Bastian (*Lancet*, 1890, vol. i., p. 1164) says: "Thus, when there is a slight lowering of functional activity in the auditory centre we have produced a slight amnesia, with forgetfulness of names of persons and things, the centre not being sufficiently active in this condition to respond to some volitional and associational incitations," and I would remark that in collæmia not a few other centres on which activity of mind and body depend are in a similar condition of lowered functional activity.

Now, a certain amount of this amnesia is one of the most common accompaniments of the headache and mental depression which are due to collæmia, and the centre which, according to Dr. Bastian, is affected cannot be very far from that to which Dr. Buzzard attributes vertigo.

And speaking of similar conditions, Sir W. H. Broadbent says (*Pulse*, p. 249): "There may, for example, be a fugitive aphasia or amblyopia or hemiopia, which are easily explained by stasis or ischæmia in certain vascular areas, but incomprehensible as the results of a poison circulating everywhere through the brain," which I should translate by saying that uric acid, by its effects on the vessels, produces the "stasis or ischæmia," which is the cause of the symptoms in these and similar conditions. The whole brain, and for that matter the whole body, is affected in much the same way, but certain parts, possibly owing to local conditions of ana-

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tomy, function or nutrition, are specially affected and give rise to special symptoms.

An interesting case of periodic stammering, having probably an identical pathology with several of the above-mentioned conditions, is recorded in the *British Medical Journal*, 1893, vol. ii., p. 1311, and I have often noticed that stammerers are decidedly worse when they are a little out of sorts, which is generally equivalent to the presence of more or less collæmia.

Hence it is only those people who have these anatomical or physiological peculiarities who suffer from headache, epilepsy, or vertigo, as the effects of uricacidæmia, while others with as much uric acid may almost entirely escape. As regards migraine, I have suggested (*Brain*, 1893, p. 250) that the possession of large arteries of supply may render some more liable than others to suffer from the intra-cranial effects of high blood pressure; this in part accounting for the fact that migraine is more common among those who work with their brains than among those who work with their muscles.

The relation of this headache to gout is very interesting, and can be easily explained, and Dr. Liveing, Sir A. Garrod, and others have recorded cases in which severe headaches of this kind unexpectedly cleared up on the supervention of an attack of gout, sometimes the first attack in the toe.

Now nothing can be more simple than the explanation of these facts. The urate cannot be in two places at once, and when local injury, plus rise of acidity, causes it to be precipitated on the toe joint, the blood is more or less quickly cleared of the excess it had previously contained; hence the headache, slow high tension pulse, cold surface and extremities, mental depression and scanty urine vanish, and pain and inflammation in one or more joints, with low tension pulse, free capillaries, and a certain amount of fever take their place, and with these, even in spite of some pain, the mental condition is more placid and the urine more profuse.

So far as my experience goes, patients generally have headaches early in life and gout later, but not the two together, though patients with well-marked gout may occasionally have severe headaches.

The headache occurs when the conditions tending to the plus excretion of uric acid predominate; the gout attacks occur when the conditions tending to its retention and accumulation predominate. Once urates are extensively deposited in joints they tend to go on accumulating there, for uric acid, as we know, attracts uric acid, so that the blood is kept pretty free, so long as there is no marked and

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continued fall of acidity; but when the patient becomes old and feeble, acidity falls greatly, and the process is reversed; there is no gout but an excessive excretion of urate, and the signs of uric-acidæmia, headache, depression, slow pulse, &c., are severe and well marked. And it is no very difficult matter to imitate nature, and produce either gouty arthritis on the one hand, or uricacidæmia and headache on the other.

Depending as this headache appears to do on the intra-cranial effects of high blood pressure, it seems evident that anything which lowers blood pressure will do good and make the headache less frequent and less severe.

Now blood pressure varies, as we have seen, chiefly with two factors: (1) the obstruction of the capillaries, and (2) the power of the left ventricle of the heart to overcome the intra-arterial pressure at each systole.

Therefore, blood pressure can be reduced by two things, namely (1) anything that will free the capillaries from globular or colloid urates about which so much has already been said, and (2) anything that will weaken the left ventricle and prevent it discharging the whole of its contents into the aorta at each systole.

It is obvious, then, that not only will all drugs and diet which reduce the uric acid passing into the blood or directly clear it out of the blood do good by allowing the capillary circulation to go free, but drugs or conditions which tend to weaken the left ventricle of the heart will also prevent or relieve the headache by reducing blood pressure. And the drugs which are classed as depressomotors may, I think, reduce blood pressure in this way, partly by reducing the power of the muscles in the walls of the arterioles, and partly by a similar depression of the heart muscle. Now such drugs as tobacco, ipecacuanha and antimony may very probably act in this way, and it is interesting to note that Dr. Liveing records (prev. ref.) that some of them have been used with good effect in migraine.

Further, it is well known that as sufferers from this headache begin to grow old, their attacks may become both less frequent and severe, or may entirely cease. Now such people, I am inclined to think, have some relative weakness of the heart, so that the pressure necessary to produce migraine can no longer be maintained.

I shall probably be reminded by pathologists that the wall of the left ventricle grows thicker with advancing age; this shows, no doubt, that the heart has more to do at 65 than at 35, but not that it does it better at the former age than at the latter.

A case in which I was much interested a few years ago furnished,

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I think, what was probably an instance of this. After years of periodical suffering, in extreme old age, with marked signs of debility, the headache disappeared, but was replaced by more or less periodical attacks of palpitation, that is to say, whenever there was collæmia and the capillaries were obstructed, the heart failed and palpitated and could not keep up the pressure (see fig. 36). In this case there was no doubt about an excessive excretion of uric acid, as the patient was greatly troubled with uric acid gravel.

While speaking of this, I may say that I have several times seen cases in which migraine has been treated more or less decidedly with antipyrin, and has remained absent for some little time after it; in one such case an irregularity in the action of the heart dated from a large dose of antipyrin taken for headache; and in one or two other cases I have found fairly marked signs of cardiac failure, which there was nothing but the antipyrin to explain, and I think we must not lose sight of the possibility that antipyrin, if pushed, may weaken the heart and thus keep off migraine for some considerable time.

When, on the other hand, a migraine, which has been habitual for many years of life—once in a month or oftener—suddenly becomes more frequent and severe, make quite sure that you have not to deal with the onset of nephritis; I have several times been misled in this way till I examined the urine. Nephritis (as we shall see in chapter xiii.), generally means chronic uricacidæmia, hence the uric acid headache will become more frequent and severe contemporaneously with its onset, will be more difficult to treat and less amenable to drugs and diet. As will also appear in chapter xiii., I regard collæmia as the chief contributing cause of the nephritis, though where this complication has supervened it will make the blood condition still worse. I have been much interested to see that Dr. Gee in a recent clinical lecture[1] describes a form of chronic headache related to gout and to migraine, and which he says is "commonest in men in adult life whose energies are just beginning to fail." Now this is exactly the time of life at which migraine tends to pass into Morbus Brightii, and there may be for a time more or less chronic uricacidæmia (collæmia). It is most often seen in men because their hearts are originally stronger and can keep up the pressure for a longer time; when they get still older their hearts fail like those of women, and then (as in the case previously mentioned) they get palpitation in place of headache.

[1] *St. Bartholomew's Hospital Journal*, June, 1897.

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If there is no sign of Bright's disease look for morbus cordis, which may intensify the bad effects of uric acid on the circulation, or failing this, inquire for recent severe illness, new growth, shock, or other cause of failing nutrition.

I recently had an illustration of one of these points in the case of a lady who came to me with all the signs of chronic collæmia. I could find no morbus cordis, though she had the cardiac signs of collæmia; I therefore suspected the kidneys, but there was no albumen. I had to confess that I could not account for the symptoms, but a few months later it became evident that she was suffering from cancer of the œsophagus, and this had no doubt been the cause of her low nutrition and collæmia.

I mention this here because it is necessary to bear in mind that the uric acid headache associated only with functional disturbance is a very different matter, both as to prognosis and treatment, from that which is associated with organic disease.

The functional trouble is rather a warning or danger signal—a sign of temporary high blood pressure and that something had better be done to relieve it—than a sign of actual disease, and with a little attention to diet it may be permanently and completely relieved.

The migraine associated with organic disease is always more serious, it may be a later stage of the functional trouble, or the organic disease (nephritis, morbus cordis, arterial degeneration, &c.), may be a co-result of more or less chronic and unrelieved collæmia; but whatever its exact origin, the treatment is now that of the organic disease, and if we succeed in relieving this the migraine will improve along with it.

In this latter case, however, success is much more difficult to attain, and unless functional and organic cases are clearly distinguished, which cannot be done without great care, the treatment I suggest may get less credit than is due to it.

Diagnosis.—When there is a paroxysmal headache lasting from six to thirty-six hours, which has recurred every seven to ten or thirty days for many years, which is accompanied by a slow high tension pulse, and a scanty excretion of urine, with marked coldness of the skin and extremities, which in a female very frequently occurs in relation to the menstrual epoch, or in a male is apt to follow the day after some unaccustomed muscular exertion, or sexual intercourse, there can hardly be much doubt about the diagnosis.

Organic headaches sometimes resemble migraine; but the paroxysmal history is absent, and when a headache has lasted more

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than thirty-six, and certainly when more than forty-eight hours, migraine should be considered very doubtful.

I have seen at least one case of hemicrania or migraine where the trouble was organic and not due to uric acid, here there was a complete absence of the paroxysmal history, and the pain lasted right on for several days; one such case was relieved by large doses of iodide of potassium, but there was no specific history.

The indications for treatment are—(*a*) *during the attack* to clear uric acid out of the blood as quickly as possible by means of any of the drugs which have this effect. One of the best ways is to take calomel, finely divided with sugar of milk, say gr. ½ at once, and gr. ¼ in an hour's time, if the headache is not decidedly better. If there is nausea or vomiting put a mustard leaf on the epigastrium for twenty to thirty minutes before using drugs by mouth. A small injection of morphine may relieve the head where there is deficient gastric absorption, or temporary relief may be obtained by compressing the carotid; (*b*) *Between attacks*, to diminish the amount of uric acid introduced in food by avoiding animal foods, soups, and extracts which are rich in it (see chapter xvii.), also strong coffee, tea, and vegetable alkaloids, and to clear out any accumulations of uric acid already existing in the body, which may be best accomplished by a course, or several courses, of salicylates at intervals. It is necessary to cut out all animal food except milk and cheese, in order to get the best results; and then milk, bread stuffs, and cereal foods with cheese, pulses and gluten must be increased so far as is necessary to replace the animal food left off. If this is done properly there need be no fall of urea, which I take as the guide of nutrition, and try to keep between 3 and 3½ grs. per pound of body weight, per day, for an adult.

If urea does get too low, the patient will be unfit for work and more or less weak, neurasthenic and miserable, and when as the result of habit he is really unable to take sufficient milk, bread and cereal foods to supply the required nitrogen, he must be given so much meat, egg or fish in addition as will suffice to keep his urea at the proper level, in the hope that his migraine will be better on this diet than on ordinary diet. On the other hand where appetite is good, and milk, bread and cereals and a small quantity of pulses are eaten heartily, there will be no difficulties with urea or nutrition, and the best results as to uric-acidæmia and migraine will be obtained.

In many cases, as in my own, change of diet is all that is necessary, and I get numerous reports of cases where this has been

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so. Dr. Logan, of Ecclefechan, N.B., kindly mentions several. In some there were "bilious attacks, with headache, sickness, rigors, and diarrhœa," and in others headache and sickness of many years' standing, all being practically cured by diet; and of one of these he says that when out at dinner or a dance "if she takes a meat dish to save being remarkable she always suffers headache and depression within two days," the exact parallel of my own experiences (similar cases are also recorded by Dr. Eskridge and Dr. Ferguson. See references in chapter vii.).

I have recently heard from my friend, Dr. W. Young, of Wellington, N.Z., the following very interesting history of a man he had met.

He noticed while on the voyage to New Zealand, that one of his fellow passengers took no meat, and on getting into conversation with him he found that he had abstained from it for eight years, because of the cruelty which meat eating inflicts upon animals, and the degrading occupation to which it exposes a large number of men.

Dr. Young then enquired as to the effects, if any, of the change of diet on his health, and was told that this had been much better of late years than previously, and that he had given up alcohol of which he had before taken freely, but without intoxication, at the same time with meat.

While a meat eater he had been subject to bilious attacks with severe headache, coming sometimes as often as once a week, but from the time of the change of diet the attacks gradually diminished in number, and are at present quite rare.

Dr. Young adds that he seems well nourished, but that he takes some animal food in the shape of eggs and milk, and my impression is that if he cut out the eggs he would remain well nourished, and have no bilious attacks at all. I am interested to see also that even Dr. Herringham[1] finds that abstinence from meat cures migraine, though he objects as much as ever to the theory that explains its action: but he refrains like other objectors from tendering a better explanation, and falls back on generalities about assimilation, which are of no use to anyone. It certainly seems to me that when the investigation of any disease has arrived at such a stage that it can be produced at pleasure by swallowing known quantities of definite chemical substances (xanthin or uric acid), and when certain cure can be effected by leaving these substances out of the diet list, there is not much room for further theorising as to causation.

As regards treatment by drugs we must not forget the action of

[1] *St. Bartholomew's Hospital Journal*, 1897, vol. i., p. 99.

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bicarbonate of soda previously referred to, as it certainly sometimes relieves both headache and depression in a very marked manner, and it probably does this not by diminishing the uric acid in the blood, but by altering its solubility, and perhaps preventing it from assuming the colloidal form; that is to say by carrying the reaction of the blood to the alkaline side of the collæmic point (see chapter v., p. 149).

Thus two or three bicarbonate of soda lozenges will often make the difference between the presence or absence of slight headache and depression, and they are specially likely to act well in warm weather in summer just at the time when salicylates are not likely to act well: the high alkalinity of the blood met with in warm weather is favourable to the action of the bicarbonate, unfavourable to that of the salicylate, and we already know that the effects of salicylates on blood pressure depend on the alkalinity of the blood, the quantity of uric acid they meet with, and probably upon the compound they form with it.

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CHAPTER VII.

Epilepsy, Convulsions, and Hysteria.

What I have just said as to the probable mode of production of the uric acid headache applies almost word for word to the causation of its near relative, epilepsy.

Thus du Bois Reymond, whose vaso-motor explanation of migraine has been quoted, goes on to speak of epilepsy as follows: "Singularly enough, if Kussmaul and Tenner's doctrine is right, which places the origin of many epileptic seizures in a spasmodic constriction of all the arteries of the head, then my migraine would be distinguished from this kind of epilepsy less by the nature of the disturbance which prevails in it, than by its degree and extent" (quoted by Liveing, "Megrim and Sick Headache," p. 300). And Dr. Liveing himself remarks, in speaking of epilepsy (p. 205), "This is doubtless the particular neurosis which exhibits the closest connection with megrim both in the occasional replacement of the one affection by the other, and also in the occurrence of cases of a character intermediate between the two."

It was my meeting with these views and quotations in Dr. Liveing's work that set me to look for a uric acid fluctuation in epilepsy similar to that I had already found in headache, and my results in one of the first cases I was able to investigate with sufficient care were published in the *Neurologisches Centralblatt*, March, 1888, and they showed that in seven hours preceding the fits the uric acid excretion was very small, having a relation to urea of only 1 to 50, in spite of the fact that these hours included the alkaline tide after breakfast, when the excretion of uric acid should normally have been large; and just as in the case of the uric acid headache, the uric acid thus held back in what should have been the alkaline tide found its way into the blood later in the day, and produced the fits; the uric acid excretion rose with each set of fits and fell in the interval between them, and with the most severe fits which occurred in the early morning hours of the following day the

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uric acid rose very high above urea, having the relation to it of 1 to 20, and when the fits finally ceased it returned nearly to normal (level of formation) 1 to 33.

Here, then, we see a series of epileptic fits corresponding to a headache, like it, preceded by a minus excretion of uric acid, which in both cases is accompanied by feelings of happiness, well-being, and mental brilliancy (due to absence of uric acid from the blood); like it also accompanied by an excessive excretion of uric acid, which is to a considerable extent proportioned to the severity of the fits, and like it also, in that when the fits cease the excretion of uric acid falls quietly to the level of formation; the plus excretion during the fits exactly balancing the minus excretion that preceded them.

Will it be considered that I was very rash in concluding, as I did from these facts, that the fits were due to the uric acid fluctuation? I confess that if I had had no previous experience of the uric acid headache, if I had not known that I could produce it or remove it at pleasure by influencing uric acid, I might have drawn a different and, I believe, less correct conclusion as to the causation of some of the fits of epilepsy. I have elsewhere quoted from Dr. Ross ("Diseases of the Nervous System," ed. i., vol. ii., p. 916), notes of a case which show that epileptic fits may be preceded by just the same feelings of happiness, well-being, and mental brilliancy that have been observed in the case of headache—symptoms which in both diseases are due to the same cause, and in both are contemporaneous with a minus excretion of uric acid in the urine, its relative absence from the blood, and the result of this a free circulation in the tissues.

I have to thank Dr. A. Sangster for reminding me that George Eliot suffered greatly from migraine, and eventually died with chronic morbus brightii, its natural ending, and that she also had a saying, "I am dangerously well to-day," meaning no doubt well-being before a headache.

Epilepsy resembles uric acid headache in the mental brightness and well-being, with scanty excretion of uric acid, which may precede both, in the excessive excretion of uric acid and mental depression which accompany both, and in the subnormal surface temperature (also due to uric acid) which may be found with both, and in both the pulse may be slow and faltering, as it often is when the tension is high (see also M. Ch. Féré, *Progrès Medical*, vol. i., 1889). Both come on early in life and last for years, both are periodical, recurring at more or less regular intervals—a character

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common to other functional disturbances produced by uric acid. Both are often met with in members of the same family, or may affect alternately one and the same patient.

Both also bear identical relations to menstruation in women (figs. 30 and 31) or fatigue in both sexes (figs. 39 and 40), and fatigue will very frequently precipitate an attack of headache or fits in those subject to them, and, as the figures show, it causes the passage of an excess of uric acid through the blood.

Among drugs the action of acids, nitrites, opium, iron, and quinine is almost exactly parallel in the two disorders.

Both again bear identical relations to dyspepsia, ingestion of indigestible food, or other causes of functional disturbance which produce uricacidæmia.

It seems to me that the parallel between the two neuroses previously noted by Liveing and others could hardly be more complete; my researches also bring out the nature of the relationship of these functional disturbances to gout which had so often been suspected by previous observers.

Since I discovered that, as the observations of the above quoted authors had led me to expect, there was a fluctuation in the excretion of uric acid with the fits of epilepsy just as with the attack of migraine, I have investigated with interest all cases of epilepsy that have come in my way, and though I have estimated, or been able to estimate the uric acid excretion in only a few of these, I believe that in the great majority I have found more or less well-marked signs of a uric acid fluctuation corresponding with the attacks, such as profuse urine before or after the fits, or both, scanty urine at the time of the fits, evidence of slow high tension pulse with mental depression or dulness before the fits; then, again, their relation to menstruation, fatigue, dyspepsia, &c., is often obviously the same as in the case of the uric acid headache. Several of the cases I examined had only slight fits with momentary unconsciousness, and the urine of these never showed any uric acid fluctuation, probably because the plus excretion lasted only a very short time, and the amount of urine already in the bladder completely overshadowed it.

On one occasion, however, a case which had previously with slight fits yielded only negative results, had a very severe fit with insensibility lasting for twenty minutes. At the end of the insensibility I was able to obtain some urine, and this was placed in a glass near me while I was seeing my other patients. I noticed that it soon became cloudy, with a pale sediment which I regarded at

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first as mucus, but on closer inspection I found that the pale sediment was rapidly falling through the fluid and collecting at the bottom of the glass.

When my work was over, the urine being even then scarcely cold, I put some of this sediment under the microscope and found that it consisted of colourless lozenges of uric acid; and on estimating the specimen I found that it contained a very great excess of uric acid, its relation to urea being 1—17. Here a case which gave no visible reaction with slight fits, gave a very marked reaction when a more severe fit occurred, so that in this case also the excess of uric acid was proportional to the severity of the fits.

It will easily be understood that when the fits give no warning of their approach, it is no easy matter to separate the urine excreted during the fit, it is almost impossible to prevent there being an admixture of before and during, or after and during, which, as will be remembered in the case of headache, gave me for a long time only negative results; but once the importance of attending to this point is understood, it is easy in the case of headache to separate the urine corresponding to the headache; but in epilepsy it is always difficult, sometimes impossible. In the epilepsy case narrated in the *Neurologisches Centralblatt* the urine was drawn at the end of each fit, and in some cases at the beginning of the fit also, but even then there was some admixture of the excretion of the fits with that of the intervals.

A case will illustrate what I mean. B. B., female, aged 20. Fits began at 12 years old. Longest time without any fits, one month; has had seven or eight in twenty-four hours; they are generally at night or early morning now. Are worse at catamenial period; but has them also between the periods. Father no gout or rheumatism; used to have "bilious headache." Mother suffers from headache, &c. Maternal aunt the same. Has one brother and one sister both subject to headaches; the sister has them about once a week, no fits.

Patient does not know when fits are coming.

Bites her tongue in the fits.

Had scarlet fever at 11 years of age.

Measles and whooping-cough as a child.

Had bad fits three days ago. Catamenia present now.

There is a recent scar on right side of tongue.

Fifteen days later had a fit at 2 a.m.

Urine was saved in two lots—(1) that passed at midnight before the fit, (2) passed a quarter of an hour after the fit at 2.15 a.m.

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No. 1 was 188 cc. and showed a relative excretion of uric acid to urea of 1 to 34, and No. 2 was 97 cc. and gave a relation of 1 to 41. There was, therefore, relatively less uric acid in the period, two and a quarter hours, in which the fit took place; but it will be seen that the separation was anything but satisfactory, and No. 2 was obviously made up of the minus excretion before the fit, as well as the plus during, and the minus far outweighed in time and quantity the plus.

It is clear that even a few positive results must far outweigh such negative results as this, even if one had not the exactly parallel case of headache to argue from. I have sometimes got patients to pass water every hour of the waking day, then when a fit occurred there was never very much water in the bladder, and in some cases there might be almost none at the beginning of a fit, and so the urine excreted from the kidney during the fit would be obtained pretty pure.

Drs. C. A. Herter and E. E. Smith, who have made some interesting researches on the relation of epilepsy to the excretion of uric acid, with a view of testing my results[1] have not, it seems to me, paid sufficient attention to this question of separation.

The smallest amount of urine examined in their tables is 134 cc., and this was not at the time of an attack of grand mal. All the amounts estimated at the time of an attack of grand mal were larger than this.

Now the amount of urine excreted in an ordinary grand mal attack, lasting, including the stupor following the fit, 20 to 30 minutes, could not be much more than 30 cc.; therefore, even under the most favourable circumstances, the urine of an attack was mixed with two volumes of urine excreted before or after it, and no excess of uric acid would, therefore, be expected.

As I have pointed out, even in the case of the uric acid headache, the excretion of the whole day may show minus uric acid, while if the urine of the attack is carefully separated, it shows plus uric acid corresponding to the hours of headache (see *Journal of Physiology*, vol. xiii.). In my case of epilepsy, published in the *Neurologisches Centralblatt*, to which these authors refer, the urine of each fit was separated as carefully as possible; and I also pointed out that when the urine of the fits was mixed with that before and after them, the uric acid came out normal, while the urine secreted during the fits showed a great excess.

[1] See *New York Medical Journal*, August, 1892.

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I certainly think it is quite useless to examine 150 to 500 cc. of urine, when that excreted during the fit could not possibly exceed 20 or 30 cc.

The authors say again, on p. 234: "The latter [that is, urine passed immediately after seizures] are apt to show a higher uric acid ratio than the urines passed just before seizures; very often, however, the ratio is one that belongs within the limits of health."

This is just my result diluted, and as the quantities are not given there is nothing to show that the urine just before was not the urine of two to three hours before, *i.e.*, a mixture; or that the urine passed after the fit really corresponded only to the excretion of the fit.

Further down on the same page they say: "The excess of uric acid that is observed in epilepsy cannot reasonably be construed as the cause of the seizures." They acknowledge, then, that there is an excess, but differ from me as to the relation of cause and effect, though we shall see further on that they are now inclined to attribute more power to uric acid.

In petit mal, however, they found a distinct relation between the excretion of uric acid and the cause of the seizures, and treatment by milk diet greatly reduced the frequency of the attacks. (Prev. ref. p. 239).

This is just what I should expect, as in my writings on the subject I have not limited myself to grand mal, but have suggested that petit mal, hystero-epilepsy, and hysteria are all similarly related to uric acid.

Where attacks of petit mal are frequent I should expect a continuous plus excretion of urates; but, as I have often proved, it is useless to look for a urate reaction in a single short attack, as the separation of urine can never be sufficiently good.

If Herter and Smith will separate the urine of grand mal cases with greater precision, I have no doubt that they will get urate reactions similar to mine, and if they will also treat grand mal to the same diet as petit mal they will, no doubt, get some satisfactory results, just as others have already done.

The observations of these authors on the relationship of the fits to intestinal putrefaction are of extreme interest because they supply a further illustration of a point which I had previously noticed. Thus, in *St. Bartholomew's Hospital Reports*, vol. xxiv., p. 226, I have made the following remark: "Salicylates again may fail to be absorbed for a time from gastric irritation or other causes, and I had a remarkable instance of this in a case of epilepsy which I was treating with this drug. On several occasions the urine gave no

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reaction with perchloride of iron during the fits, though on some occasions there was probably as much as 20 grs. of the salicylate lying in the stomach, and there was a strong reaction in the urine after the fits had passed off, without any more of the drug being given."

I notice also with interest that M. Ch. Féré records (*Progrès Medical*, December, 1888, p. 452) that there is a lowering of tension in the renal vessels at the end of the epileptic paroxysm, accompanied by increased elimination of drugs, and this practically demonstrates that there was high tension and diminished elimination of drugs during the paroxysm, and exactly illustrates what I have said on the subject in reference to fig. 32.

I can now explain all the facts much more completely than I could at the time the above was written, for I now know that when uric acid in the blood raises arterial tension it obstructs the capillaries throughout the whole body; so that not only are the urine and saliva scanty, not only is the skin cold and dry, but all the gastro-intestinal secretions (gastric juice, bile, pancreatic and intestinal juices), are similarly diminished, and the circulation through their mucous membranes is so imperfect that digestion and absorption come to a standstill. This and the generally diminished metabolism accounts for the marked fall in urea excretion that generally accompanies a plus excretion of uric acid, and the resumption of these physiological processes accounts for the rise of urea when the urates are cleared out of the blood, and their excretion in the urine diminished.

But such a marked arrest of gastro-intestinal digestion will almost certainly be accompanied by the onset of putrefactive processes—the processes of which Herter and Smith have observed some of the results.

All is now clear; the reason the salicylate failed to appear in the urine in the above case was because the capillaries were obstructed, and gastro-intestinal digestion and absorption were at a standstill.

We can now see clearly the origin of the horrible fœtid dejecta often met with after an attack of dyspepsia, bilious attack, or uric acid storm; also why calomel so promptly puts matters of this kind right. I used to think that it acted directly as an antiseptic, but it is now evident that its most important action is the result of its chemical relation to uric acid, by which it clears urates out of the blood, frees the capillaries and allows gastro-intestinal digestion to proceed once more (see p. 61).

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The intestinal putrefaction noticed by Herter and Smith, far from being the cause of the fits, is but a result of uricacidæmia. The obstruction of capillaries which produces the high tension, which in turn interferes, as I have pointed out above with the intracranial circulation and produces fits, interferes also with gastro-intestinal digestion and allows putrefaction to take its place.

It is interesting to note in this connection that Agostini (Riv. di Pat. Nerv. e Ment., iii., 1896), finds that the gastric juice after an attack of major epilepsy is toxic, causing when injected into rabbits, fall of temperature, slowness of respiration, weakness and general convulsions, and suggests among other things that the stomach excretes some toxin which is circulating in the blood. It seems to me that the symptoms are not unlike those of uric acid collæmia in man, and also resemble those produced in rabbits by feeding with hypoxanthin (see chapter xvii.).

Like the uric acid headache, uric acid epilepsy is often strictly periodical. M. H., the case whose excretion in a series of fits is given in the *Neurologisches Centralblatt*, has been under my care ever since, and my notes show that in her case the fits come with considerable regularity every fourth week; occasionally there is a slighter attack at a two-week interval. Again, in this case the fits almost always come at a time when the excretion of uric acid is naturally large—as in the early morning, when the acid tide of the night has run itself out, and with falling acidity there is a plus excretion of uric acid. Then on occasions too numerous to mention, the fits in this case have been obviously precipitated by causes which would produce a uric acid fluctuation and its temporary excess in the blood.

Thus one morning in the early alkaline tide she was standing on a chair when a fit caused her to have a bad fall and cut open her chin. Chloroform was administered, and the wound was sewn up, but the chloroform upset her stomach and produced vomiting, and she had a series of extremely severe fits. Obviously the vomiting would diminish acidity and flood the blood with uric acid.

Again, this patient has often told me that though she had no warning of the individual fits, she generally feels more heavy and drowsy on waking on those mornings on which she subsequently has fits, and this is a complete parallel of the uric acid headache, the heaviness and drowsiness and disinclination for getting out of bed, being in both cases the work of uric acid, and to my mind a proof of its excess in blood. Of the heaviness and stupor that follow the fits I have spoken elsewhere (*Brain*, Spring Number, 1891, p. 83).

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and have pointed out that this also corresponds with the work of uric acid, but (as pointed out by others) is not proportional to the severity of the fits.

While speaking of this case I will just mention a few points in treatment which it appears to illustrate.

One of the first things I did after getting a uric acid reaction in this case was to put her on salicylate of soda, and for a long time she appeared to be doing very well on it, and she said that she was brighter and better in herself—a remark which is made by many epileptics when put on this drug.

The fits, however, returned, and it is doubtful whether the apparent improvement under salicylates was more than one of the natural fluctuations in the frequency of the attacks, as this drug was tried to a much larger extent by my friend Dr. Tooth, at the National Hospital, Queen Square, and though most cases were brighter and better at first they afterwards relapsed.

But salicylate of soda is undoubtedly a double-edged weapon; it promotes the excretion of uric acid, it is true, but in a disease like epilepsy this is often a cause of danger, for if the drug is taken irregularly its action may fail and leave a considerable amount of uric acid (so to speak) stranded in the blood, and if some of this gets into combination with an alkali it will produce a fit, and a headache as I know can be produced in the same way. Again, salicylate will sometimes upset the stomach when taken irregularly or at the wrong hours, and the gastric upset will not only prevent the action of the salicylate, but will bring about a rise in alkalinity and precipitate a uric acid storm.

My impression is, therefore, that in epilepsy even more than in headache diet is the only thing that holds out much hope of controlling the uric acid. In the following case it appears that diet coupled with somewhat severe purgation did put a stop to the fits, and I have previously mentioned (p. 185) a similar case from the experience of the late Dr. King Chambers, while recently I have heard from quite a number of colleagues and others, that they have put my suggestions in practice with more or less benefit to their epileptic patients; though much more experience is required before we can safely build on the results obtained, except as indications and encouragement to try the same treatment in what appear to be similar cases.

I owe the notes of this case to the kindness of a patient, who, having relations in the profession, was able to appreciate the bearing of his relative's case upon my researches; it is that of a gentle-

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man, aged 50, who had suffered from fits all his life, and was cured by a severely vegetarian diet, with a purgative dose of calomel and colocynth, followed by Haust. Sennæ co. twice a week, he lived twenty years more without any fits at all.

He lost weight very decidedly, and was considerably weakened by the treatment, and I think it probable that the urate formation and introduction were not only greatly reduced, but that the heart was also much weakened by the severe treatment, and hence was incapable of keeping up so much blood pressure as was necessary to compress the intra-cranial veins.

Probably this treatment was unnecessarily severe; at the same time there are, no doubt, plenty of epileptics who would be glad to purchase freedom from their disease at even greater cost.

The treatment in the above case was recommended by a Dr. Pelham Warren, long since dead, and the directions say, among other things, "the medicine is meant to remedy the mischief arising from an inactive state of the liver, indigestion, &c., but the constitution cannot be freed from the unhappy tendency to pressure on the brain and convulsions without the strictest persevering attention to diet."

"Pressure on the brain" is an extremely good and possibly accurate description of the real condition present, and it reminds us of what patients with headache or depression so often say—that their head is bursting, or their brains boiling over. We can now realise much more thoroughly the condition of affairs that underlies these sensations.

Among others I have heard from Dr. Logan, of Ecclefechan, N.B., of a case of epilepsy of twenty years' standing, which has apparently benefited very greatly by the diet treatment I suggested, after bromides had failed and been left off; and quite a number of cases similarly improved on a diet of vegetables and milk are quoted by Dr. J. Ferguson, of Toronto, in a paper, "Some Remarks on Epilepsy," read before the Huron Medical Association, and in a later paper (*Alienist and Neurologist*, April, 1893). Dr. J. T. Eskridge of Denver, Colorado, has written on these subjects in the *Alienist and Neurologist* for January, 1892, and I have since heard from him that he is getting many excellent results, and I cannot but regard these reports as very hopeful.

As I have previously pointed out, Sir W. H. Broadbent, in his very interesting book on "The Pulse," p. 120, says, in reference to Tripier's theories about the pulse of epilepsy: "I think it is the slowing of the circulation which causes the convulsions," and a

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little further on he says, "I look upon convulsive attacks, when they occur in connection with an infrequent pulse, as a result of cerebral anæmia, produced exactly in the same way as the convulsions after great hæmorrhage"; and again he says, "The late Dr. Moxon, it will be remembered, went so far as to suggest that the initial event in common epilepsy was a stoppage of the heart." See also an interesting paper, "Experimental untersuchungen uber Anæmie und Hyperæmie des Gehirns in ihren Beziehung zur Epilepsie" (*Archiv de Physiologie*, June, 1891, p. 609).

In this connection it is interesting to note that Dr. S. West has pointed out (*Lancet*, 1896, vol. i., p. 1478) that digitalis and belladonna are valuable additions to bromides in epilepsy, for if digitalis strengthens the heart it may suffice to prevent its stopping as the result of temporary failure before high blood pressure, see also case to be mentioned presently where hæmorrhage stopped with the onset of a fit.

Now it seems to me we have in the effects of uric acid on the circulation—about which I have said so much—a direct cause of just such alterations in the cerebral circulation as Sir W. H. Broadbent here refers to. For my part I should be inclined to state the case for the causation of fits by uric acid somewhat as follows: In 1888 I pointed out that some epileptic fits are accompanied by a characteristic fluctuation in the excretion of uric acid, in that there is a minus excretion of that substance before and after the fits, and a corresponding plus excretion during their continuance, and this observation has since been repeated by myself and others; and, as has been pointed out, very many of the signs and symptoms of epileptic and other fits are the signs of uricacidæmia.

Further, it is very improbable that the fits are the cause of the large excretion of uric acid, because this is but the natural result of a fluctuation in excretion which took place hours before the fits began. On the other hand, it is extremely probable that uric acid is the cause of the fits, because I can practically prove that it may produce such changes in the circulation (stasis, &c.) as Sir W. H. Broadbent and others believe to be the cause of fits (see p. 199 to 201, and *Brain*, spring and summer number, 1893). Exactly the same argument applies to the causation of puerperal and uræmic convulsions. Pregnancy is undoubtedly a time of greatly increased metabolism, during which there is sure to be considerable storage of uric acid which finds its way into the blood as soon as digestion and metabolism are upset by the pains, troubles, and fatigues of delivery. In Bright's disease again there is nearly always high

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blood pressure and excess of uric acid in the blood which produces it, and it needs but a slight fluctuation in excretion to produce stasis and hyperæmia in the intra-cranial circulation and possibly œdema of membranes as well.

It is very interesting to note that the value of a non meat diet in pregnancy has been already found out empirically by others, and it would even appear from what they say that many of the pains and troubles of pregnancy and childbirth are really the results of dietetic errors (see *Brit. Med. Jour.*, 1895, vol. ii., p. 99, also further on as to the causation of fatigue).

I know also from my own experience, as well as from what I hear from others, that similar diet, perhaps decided on for other reasons, has often very greatly relieved menstrual troubles, such as dysmenorrhœa and menorrhagia; and I think that it probably acts in both conditions by lowering blood pressure, and relieving the heart, and thus preventing congestion of the hepatic, abdominal, and pelvic circulations, about which I shall have to speak again in chapter xiv.

On the other hand, in some cases the pains attending the monthly period have been very distinctly worse on beginning a uric acid free diet, but this may have been due to a rush of stored uric acid through the blood at first, and I believe they get less again later on.

I believe that hysteria and hysterical fits bear the same relation to uric acid as the fits we have been speaking of, and that many of the minor symptoms of hysteria are the signs of uricacidæmia.

I have pointed out in relation to the effects of uric acid on metabolism (chapter iv.) that the passage of a large quantity of uric acid through the blood is generally accompanied by a fall in the excretion of urea (*i.e.*, probably in the formation of urea), while, on the other hand, the clearing of uric acid out of the blood by anything that quickly produces this effect is followed by a rise of urea. These urea fluctuations probably afford to some extent a measure of the effects of uric acid on metabolism, and have suggested to me that the rise of urea noticed by MM. Gilles de la Tourette and Cathlineau (*Progrès Medical*, 1889, vol. i.) as occurring at the end of an attack of hysteria is due to the same causes; thus they observe that the urea is diminished in the twenty-four hours, including the attack, and when the attack is coming to an end as the arterioles begin to get free, there is a rise of urea from increased metabolism; no doubt also the circulatory troubles which interfere with metabolism in the muscles, liver, &c., will interfere with or

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temporarily suspend gastric digestion also. The above authors also mention that there is a marked temporary polyuria affecting the first micturition after the attack, and remark that the cause of this polyuria is not completely known; but if the attack is attended, as I believe, by high blood pressure and obstructed capillaries, and if as it passes off the capillaries are freed, there is not much difficulty in accordance with my previous arguments in completely explaining the temporary diuresis (see p. 18). Probably the correct way to state the case would be to say that the freeing of capillaries which allows of a good circulation in the kidney and a diuresis, allows also a satisfactory circulation in the brain, and the mental faculties regain their normal equilibrium; it is, in a word, the circulation which acts on the nerve centres just as it acts on the skin, muscles, liver and kidneys, and perturbs their functions.

I have found excess of uric acid in the urine in some hysterical attacks, and I look upon the nervous symptoms as the results of the circulatory disturbances produced by uricacidæmia; and this same cause will account for the fall of urea during, and the rise after, as well as for the diuresis which follows the attack, which these authors acknowledge that they are unable to explain.

It seems, then, that epilepsy is not only, as has long been known, related to gout and to migraine, but it has, as I have pointed out, an important relation to the relative excretion of uric acid in the urine, an excess of uric acid in the urine being the index of an excess in the blood, and this by its effects on the vessels, may be the actual cause of such changes in the cerebral circulation as will give rise to fits.

Thus my observations and reasoning, founded on clinical relationship, appear to afford us a fairly good working explanation of the causation of these diseases.

Nevertheless I still from time to time ask myself this question, "Is the Uric Acid fluctuation a cause or a consequence of the Epileptic Fit?" And it seems to me that from whatever point of view I look at it, whether I regard the relation of the excretion to the fit, and the fact that the plus excretion of uric acid is the result of a minus excretion which preceded the fit, and could not, therefore, possibly be caused by it; or whether I regard the extensive and important series of parallels between an epileptic fit and a uric acid headache, or when I look at the very powerful effects of uric acid on the circulation, nutrition and function of many important organs and tissues, I seem to get only one answer from all sides, "cause."

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Now it follows that if uric acid is the cause of the fits we ought to be able by controlling the uric acid to control the fits to something like the same extent to which, by controlling the uric acid, we can control the uric acid headache (migraine); and I may claim, I think, for this headache that I have absolutely and completely controlled the attacks both in myself and many others, by clearing the blood of uric acid and keeping it clear.

Can the same be done for epilepsy? My impression is that it will certainly be more difficult to do, but should not be by any means impossible, though the absolute amount of control may be less in the case of the fits than in the case of the headaches.

In headache there is a large and comparatively slow fluctuation in the excretion of uric acid, *i.e.*, a man has a headache to-day, because yesterday in the alkaline tide something interfered with his urate excretion and he passed out of his body only half the quantity he usually passes in the same hours; to-day the uric acid held back yesterday adds itself on to the natural excretion and there is consequently enough in his blood for a few hours to affect blood pressure and the intra-cranial circulation.

The object I attain by diet is so to reduce the intake and formation of uric acid that the largest quantity he is likely to get in his blood as the result of such a fluctuation shall never, or only very rarely, be sufficient to affect the blood pressure and the intra-cranial circulation to a serious extent.

Now in epilepsy (as will appear from my clinical results further on) the fluctuation is shorter and steeper, for 2 to 3 hours there is a very powerful retention of uric acid during which just as in the corresponding case of headache the patient feels unusually well and strong; and this is followed in the next two hours by an equally short and sharp plus excretion of all the uric acid held back.

In a word, the epileptic wave of excretion runs very high but only for a short time and it is very difficult to keep the general level of uric acid excretion so low, that these waves shall not occasionally get high enough to do damage by raising the blood pressure and affecting the intra-cranial circulation.

I note with much interest in this connection that Dr. Gowers remarks (*Lancet*, 1895, vol. i., p. 1626) that the visual sensations of epilepsy last seconds, those of migraine minutes, while the convulsion of epilepsy lasts minutes, and the paroxysm of migraine hours.

With regard to the parallels between the uric acid headache and the fits of epilepsy, though much has been written on the

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subject it may not be altogether without interest if I shortly mention the main points again in tabular form.

Now these two diseases agree in

(1) Having no morbid anatomy.[1]

(2) Being periodical.

(3) Occurring for years or for life.

(4) Occurring together or in alternation.

(5) Being preceded by a minus excretion of uric acid accompanied as usual by feelings of well-being.

(6) Being accompanied by a plus excretion of uric acid, and bearing a generally similar relation to the natural diurnal variations in the excretion of uric acid.

(7) In being worse at or about the menstrual period in women (see figs. 30 and 31).

(8) In being better during pregnancy and worse after delivery.[2]

(9) In being better during fevers and worse after them.[3]

In 7, 8, and 9 they both exhibit a remarkable parallel with another disease which is due to uric acid, viz., Raynaud's disease (see chapter xi.), also to a certain extent with chorea, which is sometimes associated as to its onset with post-febrile or menstrual collæmia.

(10) In being preceded by high blood pressure[4] and irregular pulse, with coldness and numbness of the extremities, and shivering.

(11) In bearing similar relations to gout, rheumatism, and other uric acid diseases.

(12) In being preceded or accompanied by subnormal temperature.

(13) In being followed by a fall of blood pressure and a diuresis.[5]

(14) In being similarly related to dyspepsia and gastro-intestinal disturbance however caused.

(15) In being similarly affected by weather and changes of temperature.

(16) In being accompanied by more or less complete suspension of gastro-intestinal digestion and absorption.

(17) In being accompanied or followed by albuminuria.[6]

[1] Wynne, *Lancet*, 1893, vol. ii., 434.

[2] Oliver, *Lancet*, 1894, vol. i., 1295; see also *British Medical Journal*, 1891, vol. ii., 1120 and 1236.

[3] *Lancet*, 1894, vol. ii., 1438.

[4] Féré, *Progrès Medical*, 1889, vol. i., 415 and 434 and vol. ii., 26.

[5] Féré, *Progrès Medical*, 1881, vol. ii., 452.

[6] *Archiv. de Neurol.*, May, 1892.

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(18) In being preceded by marked changes in, or even complete loss of sight.[1]

(19) In being similarly related to peripheral neuritis.[2]

(20) In being made worse by cold.

(21) In being made worse by administration of quinine, iron,[3] or lead.

(22) In being improved by nitrites, acids, or antipyrin.[4]

(23) In being relieved by compression of the carotid arteries.

(24) In being more or less completely cured by diet.

With regard to 6, it is remarkable how these two diseases, in common with mental depression, asthma, angina and other similar troubles, tend to attack sufferers in the early morning hours; just as the acid tide of the night is coming to an end, just as the uric acid which has been for many hours below urea tends with the falling acidity to rise above it (see figs. 2 and 3); just as the low blood pressure, free capillaries and quick pulse of the night, give place to the high blood pressure, obstructed capillaries and slow pulse of the early morning, and just as the reaction of the blood changing with that of the urine from less alkaline to more alkaline, and from more acid to less acid respectively, passes through what is probably its point of greatest urate precipitation, the collæmic point (see chapter v.). And these facts have been observed by hundreds of people who did not know that the uric acid fluctuation was the cause of all the other changes, and thus missed the key that explains them all, and proves that uric acid is the cause of all these diseases.

Here, then, in the early morning hours we have a fluctuation in the excretion of uric acid very similar to that which occurs in the epileptic fit, and it is little wonder that a slight pathological increase of this fluctuation should suffice to produce any or all of the above diseases.

It follows from this reasoning also that if the blood passes to the alkaline side of the collæmic point in the later morning hours (say 8.0 a.m. and 9.0 a.m., fig. 3), it will have to pass back through the collæmic point again as the acidity rises later on about 11.0 a.m. or 12.0 noon, and this coincides with my experience that headaches may begin or return about these latter hours.

[1] Gowers, *Lancet*, 1895, vol. i., p. 1626.

[2] Charcot, *Progrès Medical*, 1890, vol. ii., 83, and Cagney, *Lancet*, 1891, vol. ii., 1095.

[3] Radcliffe, *Practitioner*, 1883, vol. xxx., p. 95.

[4] *Lancet*, 1887, vol. ii., 1163.

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The effect of the collæmia will depend partly on the amount of uric acid available, and partly upon whether the reaction of the blood tends to linger about the collæmic point, or to pass quickly through it to one side or the other; this also will explain the effects of a few grains of bicarbonate of soda, as comparatively little may in some cases be needed to turn the scale to the alkaline side of the collæmic point.

In all these respects there is the very closest parallel between the uric acid headache and the fits of epilepsy, or uræmic, puerperal and other convulsions.

If both are due to uric acid nothing is more simple than the causation of this extensive parallelism; but it is otherwise absolutely inexplicable.

An extremely interesting series of papers by Drs. J. Voisin and R. Petit on epilepsy as due to intoxication, has appeared in the *Archives de Neurologie*,[1] and I have just given a reference to a paper by Dr. Wynne, who argues in favour of similar causation. Drs. Voisin and Petit do not appear to have seen my previous writings and researches, nor have they as yet identified or named any poison, so that in this respect I am considerably ahead of them; but their argument for intoxication strongly supports my own, and, moreover, I can show that almost every point on which they lay stress can be absolutely and completely explained if it be granted that uric acid is the toxic substance, and those who have watched my results in these and other directions will, I hope, have no difficulty in admitting that it is toxic.

I shall only mention one or two points in their papers that bear on uric acid as the cause of epilepsy.

Thus the authors lay great stress on the occurrence of gastric troubles before and during the fits or series of fits, but if the series is coming to an end, then the tongue clears, and the gastric symptoms subside; if the gastric symptoms do not subside, the epileptic phenomena will continue.

The explanation of this is simple enough when we know that every gastric upset brings excess of uric acid into the blood in those who have much of it in their bodies. The gastric trouble is thus the cause of the collæmia which is the cause of the fits, the malaise, the headache, and all other symptoms, and it in its turn intensifies the gastric upset, and adds putrefaction with possible formation of toxic products.

[1] 1895, Nos. 98, 99, 100, *et seq.*

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But the gastric troubles are the result of intoxication by uric acid, even though their result is to increase the toxæmia, for in migraine, if you keep the blood clear of uric acid, both the gastric troubles and the paroxysm of headache are absent.

With regard to the urine, they point out that there is diminished toxicity before and during, and increased toxicity after the fit, and it is interesting to note the exact parallel between the excretion of uric acid (which the authors have not estimated, though they notice in one case a deposit after a fit), and the toxic substance.

The authors mention an extremely interesting case, in which a wound that was being dressed stopped bleeding with the onset of a fit, and no pulse could be felt at the wrist; but at the end of the spasmodic stage the pulse reappeared, beating 142, the blood pressure rose, and the wound began to bleed freely once more.

In this case the fit was probably due to stoppage of the heart, which failed before the high blood pressure, and with the fall of blood pressure, due to the stoppage of the heart, the circulation practically ceased, and the wound stopped bleeding, and the corresponding stasis in the cerebral circuit produced the convulsion; later on the pressure having fallen, the heart recovered itself and began beating again, and in the above case the pressure rose above normal after the fit, though probably not so high as it was just before it when the heart failed. I have seen a very large number of cases in which the heart has given obvious signs of impending failure before the high blood pressure produced by uric acid, in the uric acid headache (migraine), and these cases differ from the above case of epilepsy merely in the fact that the heart, though threatening to fail, did not fail, and so there was no convulsion. And these severe paroxysms of headache may, just like the epileptic fit, be followed by albuminuria.

Talking of albuminuria reminds me of paroxysmal albuminuria, and hæmoglobinuria, which I have long held that this albuminuria resembles (see chapters xii. and xiii.), and so of the blood changes which take place in paroxysmal hæmoglobinuria and in anæmia as the result of the presence of an excess of uric acid in the blood stream. And I have therefore been very greatly interested to see that the authors mention that a diminution of hæmoglobin and an increase of hæmatoblasts has been observed in connection with the fits, and this is a change which I thought of as probable in epilepsy, because, as I shall have to point out in chapter xii., my own blood varies its quality from hour to hour and day to day in accordance with the amount of uric acid passing through it. In the case

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to be presently related, Dr. Huntley kindly examined the blood after one or two fits, but his results were indefinite, and I was, unfortunately, not able to examine it myself, but I hope to do so in some future cases, as I have yet to learn at what length of time after the fit the blood changes show best; probably after or during the albuminuria, when present.

The authors also point out that repair of wounds is defective while the epileptic phenomena continue, and only goes on properly after the toxine has been eliminated. Here again we have the work of uric acid, for I have for years been pointing out that opium, which the surgeons use to aid the repair of skin wounds, acts by clearing the blood of uric acid, and thus allowing a free capillary circulation in the skin, which is impossible so long as the blood is full of uric acid, and in the ordinary uric acid headache, the signs of defective capillary circulation throughout the body are so obvious that they can hardly be missed, even if there is no "dead hand" or actual Raynaud's disease to draw special attention to them.

Then again, many troubles of mind and its adjustment which the authors mention are so obviously similar in migraine and epilepsy, and after what I have elsewhere shown with regard to them are so obviously due to uric acid, as to need no comment.

As regards causation, the authors point out that epileptics come of a degenerate stock and one subject to many kindred troubles and defects; one must not, I think, however, lose sight of the fact that several men whose names stand large on the pages of the past, yet suffered from epilepsy,[1] or that migraine is most common among those who work with their brains.

As to heredity and predisposition migraine is intensely hereditary, but the inheritance is probably as I have shown (*Brain*, spring and summer number, 1893, p. 250), merely anatomical, viz., the size of the arteries that supply the brain, this accounting for the absence of migraine among those who work with their muscles, and may probably have only small arteries to supply their brain.

And there is nothing extraordinary in this inheritance, for are not eyes, noses and teeth similarly inherited with an exactitude which is sometimes marvellous?

But in migraine, if you control the uric acid, you may absolutely and entirely neglect the anatomical inheritance, which is an advantage rather than a defect.

[1] Sir J. Crichton-Brown.—*Lancet*, 1895, vol. ii., p. 74.

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Epilepsy also like migraine may be in part the result of large arteries, and therefore may occur along with considerable mental power, while the eventual crippling and destruction of mind referred to by Sir J. Crichton-Browne (prev. ref.) may be a result of the repeated congestion, strain and œdema produced by the recurring high blood pressure.

It is interesting also to note that the above mentioned author observed himself, that in "dreamy mental states," which he considers as allied to epilepsy, a diet rich in animal food did harm, and he also quotes cases of epilepsy as being similarly affected by diet.

Three generations at least, in my own family have been affected with migraine, but in the second and third generations diet has absolutely and completely controlled it.

I quite agree with the authors in their argument that an accumulating poison gives the best explanation of the attacks, and I have been pointing this out for nine years and indicating uric acid as the probable poison.

The authors lay great stress on the liability of women to epilepsy at the menstrual period and the regularity with which attacks recur at each period, and their observation is of interest as confirming my own (see figs. 30 and 31).

If the facts I have brought forward regarding the relationship between the fits and excretion of uric acid stood alone, they would be worthy of very careful consideration, but linked as they are to the similar facts about migraine, and the further fact of its control and prevention by controlling the uric acid, they amount almost to a demonstration of the causation of epilepsy.

The authors divide epilepsy into (1) Reflex, and (2) Toxic; the latter is further sub-divided into (α) that due to auto-intoxication; (β) that due to hetero-intoxication.

Obviously uric acid may account for toxic epilepsy of auto-intoxication, but even here my researches show that a large part of the required uric acid was formed outside the body and merely introduced with the food. Having all these points in mind, and believing very strongly in the uric acid causation of epilepsy either as the result of the blood pressure and circulation changes it produces in the skull, or of the heart failure and consequent stoppage of the circulation it causes by blocking the capillaries in general, as in the case just quoted, I decided to investigate the following case, controlling the uric acid as carefully as possible and watching whether the fits would respond in any way.

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Emma S., aged 20, admitted under my care at the Royal Hospital for Children and Women, on December 7, 1894.[1]

Her fits began when she was fourteen years old. At present they are very regular once a week, and often on the same day each week. Her monthly periods began at fifteen years of age, and are said to have been regular (but as we shall see, they did not occur during her stay in the hospital). Her father and mother are alive and well, but her mother suffers occasionally from headache. Has eleven brothers and sisters in good health.

I examined the urine excreted before, during and after a large number of her fits, and got uric acid fluctuations identical with those I had found in other cases, or in that first published (prev. ref).

She was kept in bed to avoid fluctuations from muscular exertion or changes of temperature, and then her diet and drugs were altered from time to time with a definite object and according to a pre-arranged plan, for controlling the introduction, formation and excretion of uric acid.

It will probably suffice if I give the excretions of only one or two fits, as most of them were practically identical, and in all, without exception, there was a very large excretion of uric acid in the hour following the fit, having a relation to urea of from 1—20 to 1—8.

During the daytime she passed water as far as possible about once every hour, so that when a fit occurred there would be but little admixture of urine in the bladder.

Then if a fit occurred, say at 3 p.m., we had got the urine passed at 2 p.m., and this was called *before*. A catheter was passed at the time of the fit, and what it brought away was called *during*, and then water was drawn or passed exactly one hour after the fit, and that was called *after*.

After always contained an excessive amount of uric acid, both absolutely and relatively to urea.

Before generally contained a normal or subnormal quantity.

During sometimes contained a considerable excess, at other times only a slight excess, according as the separation corresponded more or less accurately with the changes of secretion: thus if urine was passed at 4 p.m., and if just as urine was going to be passed at 5 p.m. a fit occurred, then the 5 p.m. urine might be called *during*, but would obviously be mixed with the excretion of say three-

[1] This case and some of the above arguments will be found in *Brain*, part lxxiii., 1896.

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quarters of an hour preceding the fit in which the excretion was small.

But bearing these causes of fluctuation in mind, one always got a great excess of uric acid in the hour after the fit, and a more moderate excess in the urine drawn at the time of the fit.

Thus on the day of admission she had a fit.

Before, passed at 2.15 p.m., pale straw coloured, 1009, gave—

Acidity = 1·0 cc. of decinormal soda solution.
Urea ... = ·75 per cent.
Uric acid = ·03360 ,,
} 1—23 = 1 of uric acid to 23 of urea (nearly).

During, drawn off at the time of the fit, at 4.45 p.m., turbid, 1012, gave—

Acidity = 1·2 cc. decinormal soda.
Urea ... = 1·0 per cent.
Uric acid = ·06048 ,,
} = 1—17 (nearly).

But obviously there was a mixture of *during*, with the urine of two and a-half hours before the fit.

After.—Urine drawn at 5.45 p.m., one hour after the fit, was 60 cc., amber, turbid, 1020, and gave—

Acidity... = 7·6 cc. decinormal soda = 4·4 grs. per hour of acidity, calculated as oxalic acid.
Urea ... = 1·1 per cent. = 10·1 grs. urea.
Uric acid = ·10080 ,, = ·92 ,, uric acid.

Relation uric acid to urea, 1—11.

February 27, 1895.—Urine of twenty-four hours, ending this morning, was 1275 cc., turbid, 1014, and gave—

Acidity... 4·0 cc. = 49·2 grs. in twenty-four hours, = 2·0 grs. per hour.
Urea 1·8 per cent. 351 grs. = 14·0 grs. per hour.
Uric acid ·04704 per cent. = 9·1 grs. ·37 grs. per hour.
} 1—37.

On this day she had a fit, and the urine *during* was lost, the specimen *after* was saved, and was the excretion of exactly one hour.

It was 57 cc., amber, slightly turbid, 1022, and gave—

Acidity ... 8·4 cc. = 4·6 grs.
Urea ... ... 1·8 per cent. = 13·8 ,,
Uric acid ... ·13440 ,, = 1·03 ,,
} 1—13.

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This shows, as compared with the hourly excretion of the day before the fit, that urea was very slightly diminished after the fit, while uric acid was nearly three times as much after the fit as before it.[1]

We see, then, that the urine after a fit has generally these characters; it has a high sp. gr., often very high as compared with *before* and *during*. It is often turbid, and deposits urates or uric acid, or both. It is highly acid, this being I think entirely due to the large amount of uric acid (often free uric acid) which it contains, and showing nothing whatever as to the alkalinity of the blood, which is probably high at the time of such a large excretion of urates.

Take another example, March 10, 1895.

Urine of 24 hours, slightly turbid, 1014.

Urea	1·6	per cent.	1—44.
Uric acid... ...	·03696	per cent.	

Urine 4 hours before the fit 1010.

Urea	·9	per cent.	1—34.
Uric acid... ...	·02688	per cent.	

Urine drawn at time of fit containing of course also the excretion of the previous 4 hours.

Acidity	·88	cc.	1—40.
Urea	1·2	per cent.	
Uric acid... ...	·0302	per cent.	

Urine one hour after the fit, pale amber, turbid, 1022.

Acidity	5·6	cc.	1—20.
Urea	1·0	per cent.	
Uric acid... ...	·05040	per cent.	

Here we have a diminished excretion 1—44 in the twenty-four hours preceding the fit, a slightly increased excretion 1—34 in the urine passed four hours before the fit.

A diminished excretion in the urine drawn at the time of the fit being also the excretion of the four hours preceding it, 1—40 showing that there was a fluctuation in the direction of minus excretion in the hours immediately preceding the fit.

And lastly, we have a plus excretion in the hour following the fit, this being, I think, probably composed of a very large excretion in the 20—30 minutes following the fit with a lessened excretion

[1] Compare with the causation of fatigue in chapter viii.

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after this, the differences in the suddenness and steepness of the waves of fluctuation accounting for the differences in relation found after different fits.

With regard to the large excretion *after* the fit, we must bear in mind that it is the uric acid in the blood that alters the blood pressure and affects the intra-cranial circulation; and it is only after it has been in excess in the blood for some little time that it begins to be found in excess in the urine.

As regards effects on the blood pressure and intra-cranial circulation, these are probably most marked just at the time of change from low to high pressure, hence the fit comes early in the uricacidæmia, and precedes the great excretion of uric acid.

See again March 19, 1895, urine of twenty-four hours, ending 8.0 a.m., 1—24.

Urine at 9.15 a.m., 1—56.

Urine at 12.15 p.m., time of fit 1—70.

Urine after fit 1.15 p.m., 1—9.

Here we have a rather plus excretion on the day before the fit, a considerable retention before 9 a.m., a greater retention between 9 and 12, followed by a very greatly plus excretion between 12 and 1 p.m.

Evidently the fluctuation which produced this fit began about 7 or 8 a.m., and the retention continued and increased up to about 12 noon, then followed the opposite and resulting plus excretion, producing the fit at 12.15 and the excretion of 1—9 between that and 1.15 p.m.

The parallel between this fluctuation and that which produces the uric acid headache is almost absolute; the differences are those of time and degree only.

Now we can control the uric acid headache by controlling the uric acid to an extent which leaves little to be desired; can we control also uric acid epilepsy by the same means?

This was the question I have endeavoured to answer by observing this case, and I chose it in preference to other cases because the history seemed to show that the fits were here remarkably regular in their weekly cycle.

I examined the urine *before*, *during*, and *after* more than fifteen of her fits, and the results in all were, as regards the main points, practically identical with those given, and I would undertake to tell in any case when urine was collected in this manner which was the urine of the hour following the fit. This urine also has a characteristic which I have not mentioned, though it is of very great

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importance, viz., that when a patient is taking drugs, such as an iodide or a salicylate, which give a marked reaction in the urine, such reaction is almost completely absent from the urine passed in the hour following the fit.

I, fortunately, noticed this point in the urine of the very first case of epilepsy I examined, and I have mentioned it before in reference to the observations of Messrs. Herter and Smith on putrefaction in the intestines; and as explaining also both the oxaluria of paroxysmal hæmoglobinuria (see chapter xii.) and dyspepsia, and the presence of excess of putrefactive products from the intestines in the urine after an epileptic fit. Under these conditions, not only is there no absorption of drugs from the stomach and intestines, but putrefaction soon takes the place of digestion, and the products formed under its influence account completely for the oxalates and excess of æthereal sulphates found later on in the urine.

To suggest, as the above-named authors have, that these putrefactive products found in the urine after a fit may represent the cause of the fit is, in my opinion, to put the cart in front of the horse, make a hopeless muddle of cause and effect, and bring a pea soup fog over a clear sky. The only simple, complete, and efficient explanation is that the circulatory changes which excess of uric acid in the blood produces, affect on the one hand the intra-cranial circulation and produce the fit, and on the other the stomach and intestines and bring digestion and absorption to a standstill; failure of absorption explains the absence of the drugs from the urine, and excess of putrefaction explains the production of the products which ultimately appear there. Precisely the same thing also occurs in the uric acid headache, for when this is severe drugs introduced into the stomach produce absolutely no physiological effect, and do not appear in the urine till the headache is passing off; and if the gastric upset is continued for some time it often ends in vomiting, and the food is then found to be almost undigested, though it has perhaps been in the stomach long enough to have been completely digested and absorbed.

In all these cases if you control the uric acid you will control also the headache, the fits and the gastric upset; all will improve together, for all are due to one and the same cause—the altered circulation which is common to the whole body.

Now in the case of Emma S., on December 30, 1894, she had a fit while taking both salicylate of soda and iodide of potassium three times a day, the urine *before* the fit gave a quantity of iodide

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when a silver salt was added, and a dark purple with perchloride of iron.

Urine during gave distinctly less iodide.

Urine after with a relation of uric acid to urea of 1—10 gave no iodide of silver, and only a very slight purple with the iron.

I shall now give the whole of her fits in the form of a table, in which I shall also note the interval between each fit and the one preceding it, health, diet, drugs, and remarks, and we can thus see at a glance any variations presented by the fits and the corresponding variations in diet and drugs made with the object of affecting uric acid.

Her first fit was on December 7, said to be one week after the previous one, her health and diet were those of her ordinary life, and she was taking no drugs.

On December 10 I put her on absolute milk diet, and gave her a mixture containing perchloride of mercury and iodide of potassium.

On December 19 she had a fit 12 days after the previous one.

On December 20 I stopped the mercury and gave iodide of potassium and salicylate of soda, leaving the milk diet as before.

On December 30 she had a fit 11 days after the previous one, making 3 fits in 30 days.

On January 2, 1895, she got slight tonsillitis with raised temperature, which became normal on the 4th.

On January 6 she had a fit, 7 days after the previous one, but I think that this short interval was probably in part the result of the attack of tonsillitis, which would cause a fluctuation in urate excretion.

After the fit on January 6 the iodide was left off, and the salicylate given alone, and all drugs were left off January 12.

I now began to test the effects of diet.

On January 18 she had a fit, 12 days after the previous one, while she was still on milk only.

On January 21 fish was added to her diet, and on 24th meat was added, and she continued to take milk, fish and meat till February 11, when beef tea was added, and she continued to take milk, fish, meat and beef tea till February 16, when the beef tea was taken off, on 21st the meat was taken off, and on 25th fish was taken off, and she was again on milk alone.

She had a fit on January 31, 13 days after the previous one, and making 3 fits in 32 days. At the date of the last of these fits she had been on fish for 10 days, and on meat for 7 days.

So far, then, diet had not affected the frequency of the fits for 13

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days was the longest interval she had had, indeed, it seemed rather as if the addition of flesh food had increased the interval, and I should not be surprised if this was the case; for in the case of the

No. of Fits.	Date.	Interval.	Health.	Diet.	Drugs.	Remarks.
	1894	Days				
1	Dec. 7	7	Average	Ordinary	None	Soon after admission
1	,, 19	12	,,	Milk only	Iodide of mercury on Dec. 10	
1	,, 30	11	,,	,, ,, ...	Salicylate of soda 20th, & iodide of potassium	3 in 30
	1895		Tonsillitis.			
1	Jan. 6	7	Temp. normal on 4th	,, ,, ...	Salicylate of soda alone	
1	,, 18	12	Average	,, ,, ...	Salicylate of soda left off 12th	3 in 32
	,, 21	..	,,	Milk and fish ..	None	
	,, 24	..	,,	Milk, fish and meat	,, ...	
1	,, 31	13	,,	,, ,, ,,	,, ...	
1	Feb. 4	4	,,	,, ,, ,,	,, ...	
1	,, 11	7	,,	Milk, fish & meat, beef tea added	,, ...	3 in 17
1	,, 17	6	,,	16th. Beef tea off	,, ...	
	,, 21	..	.. ..	Meat off		
	,, 25	..	.. ..	Fish off		
1	,, 27	10	Average	Milk only	,, ...	
1	Mar. 10	11	,,	,, ,, ...	,, ...	
	,, 11	..	,,	Milk and beef tea	,, ...	3 in 30
1	,, 19	9	,,	Milk only; last beef tea 16th	,, ...	
	,, 21	..	.. ..	Tea		
2	,, 25	6	Average	Farinaceous with 4 cups tea	2-3 grs. theine per d.	
	,, 29	..	Temp. raised slightly	.. .. ..	.. .. ..	3 in 18
1	April 2	8	Average	Farinaceous and tea	None	
1	,, 6	4	,,	,, ,,	,, ...	
	,, 11	..	,,	,, no tea	,, ...	
1	,, 17	11	,,	,, ,,	,, ...	
1	,, 24	7	,,	,, ,,	,, ...	3 in 29
1	May 5	11	,,	,, ,,	,, ...	
	,, 6	..	,,	,, & tea again	,, ...	
1	,, 13	8	,,	.. .. ..	.. .. ..	
1	,, 21	8	,,	Farinaceous & tea again	None	3 in 26[1]
1	,, 31	10	,,	Farinaceous & tea	,, ...	

[1] NOTE.—The previous 3 in 18 was probably partly the result of the beef tea.

uric acid headache, taking meat steadily every day does not produce a headache nearly so quickly as taking it only for one day or one meal; and the reason is that the steady daily introduction of uric

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acid tends at first to keep the blood clear, while a single dose does not raise the acidity much, and as soon as the acidity falls it gets into the blood and produces signs of its presence.

The next fit was on February 4, 4 days after the previous one, and the next on February 11, 7 days after that, and the next on February 17, 6 days later, making 3 fits in 17 days, a very different record from the two previous series.

From February 25 to March 11, she was on milk only; on March 11, beef tea was added and continued till March 16.

On February 27 she had a fit ten days after the previous one, a second on March 10, 11 days after it, being on milk only, and a third on March 19, 9 days later when she had been on milk and beef tea for 8 days; this making 3 fits in 30 days, or the same record as the first two series.

Now came what was rather a surprise to me; on March 16, the beef tea was left off, and on March 21 she was put on farinaceous diet, which includes bread, puddings, and tea in addition to milk.

She now had a fit on March 25 (or rather 2 close together which I count as 1, as both were due to the same fluctuation of urates) 6 days after the previous one; another on April 2, 8 days later, and a third on April 6, 4 days after that, making 3 fits in 18 days.

Now as I say this was rather a surprise, for though I expected that the beef tea might have some effect, it was left off on March 16, and yet the quickest time of all was the fit on April 6, 4 days after the previous one.

I confess that at this point I felt rather at sea: but I chanced one afternoon to go into the ward just as she had finished her tea, and looking into her cup I saw that what remained was very dark coloured, and it had evidently been rather strong. This led me to enquire how much tea was included in the farinaceous diet, and I found that she had four breakfast cups a day, two at breakfast and two at tea, and further enquiring as to the amount of tea leaves used to make this amount of tea and taking it that one pound of tea contains 175 grs. of theine, I found that she was thus introducing into her body nearly 3 grs. of theine a day.

And as we have seen that caffeine, theine, theobromine and all similar xanthin compounds, are practically equivalent to uric acid (see fig. 28), she was thus quietly pouring in the equivalent of at least 20 grs. of uric acid a week.

And it was thus little to be wondered at that with the help of the beef tea from March 11 to 16 her fits had been more frequent.

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After making this discovery I stopped her tea on April 11, leaving her farinaceous diet otherwise as before.

She now had a fit on April 17, 11 days after the previous one, another on April 24, 7 days later, and a third on May 5, 11 days after that, making 3 fits in 29 days.

On May 6 she was again given tea, her diet being otherwise unaltered, and she had a fit on May 13, 8 days after the previous one, a second on May 21, 8 days later, and a third on May 31, 10 days after that; making 3 fits in 26 days, or slightly quicker than in the previous series.

I now decided that I would try and diminish the frequency of fits, so I put her on farinaceous diet without tea, and gave her salicylate of sodium with iodide of potassium, the former to eliminate as much as possible of the uric acid she might have in her body, and the second to prevent it from combining with an alkali when in the blood, for it is apparently, as I have said, the combination of uric acid with alkaline or neutral phosphates in the blood, which produces all the physiological and pathological effects which I have been led to attribute to uric acid. I also allowed her to get up, she having been in bed the whole of the previous period, about six months in all.

With this change of diet and drugs she went without a fit for a whole month, and had had no further attack when she left the hospital at the end of June.

The diet treatment did not cause any loss of weight as in the case previously mentioned, for she kept about 90—91 lbs. during the whole of her stay in the hospital.

On several occasions the temperature was lower thirty minutes after a fit, *i.e.*, when there was still plus uric acid passing through the blood, than at the same hour next day when there had been no fit (see fig. 5).

Thus on May 5, half an hour after the fit, the temperature was, in the mouth 98°; in the rectum, 98·4°.

May 6, same hour, in the mouth, 99°; in the rectum, 99·4°.

On May 31, half an hour after a fit, the temperature was in the the mouth, 98·4; in the rectum, 98·8°.

On June 1, no fit, the temperature was, in the mouth, 98·8°; in the rectum, 99·6°.

On another occasion the temperature was again slightly higher on the day after the fit, and on a fourth occasion there was no difference between the temperature on the day of the fit and on the following day.

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It is remarkable that with the uricacidæmia with and after the fits there is not a greater distance between the temperatures in the mouth and rectum; but if the collæmia was severe and the obstruction of capillaries great and general, the nutrition and combustion of the whole body might be hindered, and then there would be a diminished production of heat (see "Causation of Fatigue," chapter viii.), and then according to Marey's rule (see description of fig. 5) the two temperatures would tend to come together rather than to be wide apart, as they are in the physiological collæmia of the alkaline tide (fig. 5).

And now for a general survey of the fluctuations shown in the table.

The fits according to history were very regular—one in a week, or 3 in 21 days. After admission, on milk only and some drugs, they fell to 3 in 30 and 3 in 32 days; then animal food was put on and they quickened up to 3 in 17 days; this was left off again, and they fell to 3 in 30 days; some beef tea and tea were given, and they quickened to 3 in 18 days; these were left off, and they fell to 3 in 29 days, tea was put on again, and they quickened slightly to 3 in 26 days.

And then when tea was left off and some drugs were given, as at first, they fell lower than they had been during the whole of her previous stay in the hospital, 30 days elapsing without any fit.

There are no doubt some who would argue that this was all pure chance, and that her fits would have varied in much the same way if no alterations in diet or drugs had been made.

I can only say that such an argument has little in it to recommend itself to my mind, for it almost passes the bounds of possible chance that the fits should by accident have varied in such remarkable correspondence with the changes we made in the uric acid introduction.

It leaves out of count also entirely the numerous cases in which a diet free from flesh food has produced a more or less marked alteration in the number of fits,[1] or a diet in which the flesh is only reduced, has produced a distinct reduction.[2]

I have seen it suggested that meat food acts as a general stimulant to the nerve centres, like corn in the food of horses; but in the uric acid headache (migraine) this is certainly not the case, as this headache is not influenced at all by the general

[1] *Lancet*, 1895, vol. i., p. 96.
[2] *British Medical Journal*, 1895, vol. i., p. 1088 and 1420.

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level of nitrogenous excretion, but only by the height of uric acid above urea, which is a measure of the quantity of uric acid passing through the blood; and this headache can be produced by the ingestion of uric acid or xanthin compounds equivalent to it, which increase the excretion of uric acid, but hardly affect total nitrogen; and in the above case it rather appears as if beef tea and tea, which introduced xanthin and uric acid, had a similar effect on the fits of epilepsy. On the other hand, in migraine you may keep urea well on the physiological level (3½ grs. per pound of body weight per day), and provided you do this with milk and vegetable substances, which do not introduce much uric acid, there will be no increase of headache (see also fig. 65 and remarks on it).

The point about migraine beyond which there is no appeal, is that if you control uric acid you control the headache, without attending to anything else; I am suggesting that the same will be found to hold for epilepsy, only here the control must be more powerful and complete, and may be correspondingly more difficult to obtain.

It further takes no notice of the fact that it is almost impossible to regard the uric acid fluctuation above described as a consequence of the fits, while it is easy, looking to the important influence which this substance exerts on the nutrition and function of almost all the tissues of the body, in the uric acid headache for instance, to regard it as a cause.

Then I believe that as a matter of fact there are really to be met with all gradations, from a mere temporary absence of mind up to a severe epileptic fit, and nothing is more common than slight absence of mind in mental depression, or the uric acid headache (see also Sir J. Crichton-Browne, *Lancet*, 1895, vol. ii., p. 4, for many interesting connections between dreamy mental states, migraine and epilepsy).

In the uric acid headache reasoning is difficult and has to be forced, and the mind becomes a complete blank for words or for names, which in ordinary conditions one knows almost as well as one's own; on the other hand, either before or after the headache, when the blood is cleared of uric acid, there is mental brightness and well being, a feeling of pleasure in living and thinking, and work is done at double speed and with comparatively little trouble: and all these things, I can answer for it, vary absolutely with the uric acid in the blood.

What I said about the association of the uric acid headache with nephritis applies also to epilepsy in any case that is due to uric acid, for nephritis means chronic collæmia, and with this the fits will

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be more frequent and severe and less amenable to drugs and diet, than in cases where the kidneys remain sound. Do we not get here also a side light on the causation of the headache and fits of uræmia? As I have pointed out, the treatment of collæmia removes the symptoms of uræmia (*Brit. Med. Jour.*, November 30, 1889, and see also chapter xiii.).

I owe to the kindness of Dr. C. Mordhorst, of Wiesbaden, the notes of a most interesting case which occurred in his practice.

It was that of a lady whose knee and foot joints showed large deposits of urates, and who was ordered to take, in addition to hot baths, a strong alkaline water (Wiesbaden gout water).

One day she took more of the water than had been ordered for her, and at midday she had a very severe attack of epilepsy, the first she had ever experienced.

Dr. Mordhorst had her urine collected, and found it to give a relation of uric acid to urea of 1 to 15.

In another case Dr. Mordhorst put a patient who suffered from epilepsy (1 to 2 attacks in a week) on two bottles of Wiesbaden gout water a day, and while she took this quantity the attacks discontinued.

She has now been on this treatment for three years always with the same good results, but if the water is left off the attacks return.

This is very interesting and reminds one of the value attached to the use of alkalies as additions to the bromides in epilepsy, by the late Dr. Radcliff (*Practitioner*, 1883, vol. xxx., p. 95). Dr. Radcliff used potash salts, and Dr. Mordhorst soda salts, but probably the effect was in both cases the same.

In the case of the above-mentioned lady the alkali met with a large amount of urate in the body, and brought into the blood on the day of the attack more than it could hold in complete solution, hence there was for a time considerable collæmia, resulting in high blood pressure, sufficient to produce a fit.

In the other case where the alkali was taken steadily for years, the quantity of uric acid to be acted on was probably never so large, and the alkali not only provided for a steady excretion of uric acid preventing fluctuations (the great causes of attacks both of headache and epilepsy), but it was able to hold the whole of the uric acid passing through the blood in fairly good solution (see remarks in chapter v.), so that collæmia was never severe, but as soon as the alkali was left off, fluctuations in excretion again returned, and these presently sufficed to reproduce the fits.

And it is just, I may remark in passing, by producing such

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fluctuations in urate excretion as are seen in fig. 13 that lead and other metals produce fits and do harm in epilepsy; and apart from the action of any metals, similar fluctuations are evidenced by the feelings of well-being, which often precede the onset of a fit, so often in fact that patients have themselves got to look on them as warnings. I also owe to Dr. Mordhorst the copy of a paper by Dr. Ackermann, "Zur Atiologie der Epilepsie," from *Zeitsch. fur die Behandlung Schwachsinniger und Epileptischer*, 1897. Nr. 2.

In this paper reference is made to Dr. Mordhorst's cases and to my writings in this book and in the *Neurolog. Centralb.* on epilepsy, and it is suggested that the cause of this disease is direct irritation either of nerves or nerve centres by uric acid which is thrown down by a local or general diminution of the alkalinity of the blood.

The natural outcome of this etiology is the treatment of the disease by alkali in the form of Wiesbaden gout water, and several cases are related showing improvement, though some are, just as we shall see to be the case with diet, worse at first and better later; no doubt in these cases there was at first too much uric acid for the alkali to hold in complete solution.

There are several points, however, in the above etiology with which I cannot agree, and it also, in my opinion, fails to explain all the phenomena.

How, for instance, can any local irritation of nervous tissues account for the pain of headache or its very obvious relation to position and blood pressure? How can we explain the action of nitrites in relieving headache or epilepsy or the value of compression of the carotids, or again, the use of venesection in uræmia? It is true that this latter may remove a small portion either of the acid or uric acid, but its most obvious effect is surely that on blood pressure.

Then again, acids are often decidedly useful both in epileptic fits and in the headache and drowsiness that precede or follow them, and the nitrites also diminish the alkalinity of the blood. It seems to me, therefore, that the only possible explanation of all the phenomena is that the fits are due to high blood pressure with or without heart failure; that the high blood pressure is due to collæmia, which again is dependent on the quantity of uric acid available and its complete or incomplete solubility in the blood, which explains the observed effects of the alkalies used.

Among points of interest in the above paper I notice that Dr. Ackermann insists strongly on the absence of demonstrable changes

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in the anatomy of the nervous system, and the impossibility of reconciling any such changes with the irregular phenomena of the attacks.

He is inclined to think, however, that epilepsy cannot be explained without a disposition to formation of excess of uric acid, or the uric acid diathesis, and he is also in favour of a special disposition on the part of the nervous system in pregnant women during and after labour, and in children; but as I have pointed out, all these points can be explained by the influence of these physiological conditions on the formation, solubility, and excretion of uric acid, and that if there is any disposition on the part of the nervous system it has reference only to the size of the arteries that supply the brain.

In this connection also he refers to the difficulty in explaining the absence of uræmic phenomena in cases of anuria, but here again, though the blood may contain excess of urea, it will also probably contain plenty of acid salts, it will therefore remain at least for some time but a poor solvent of uric acid, and there will be no severe collæmia and high blood pressure such as occurs in uræmia, till near the end; then with a general failure of nutrition and strength the blood becomes again perhaps a good solvent of uric acid, and more or less collæmia results.

He lays great stress on the many points of resemblance between uræmia and epilepsy, and there are obviously still more points of resemblance when we consider also the headache, the eye-symptoms, and the blood pressure changes.

I am indebted to Dr. A. J. Hubbard, of Hemel Hempstead, for the interesting suggestion that the convulsions of bottle-fed infants are partly due to the fact that in taking cow's milk, which contains one-third more casein than human milk, they are relatively on a highly nitrogenous diet (see fig. 65). Dr. Hubbard has also found that salicylate of soda is of far more value in the treatment of these troubles than the alkalies which are commonly prescribed.

Diagnosis.—The time has not yet arrived for any dogmatic statements on this point; but where epileptic fits have recurred with more or less regular periodicity for a long time, and also resemble migraine in their relation to dyspepsia, muscular exertion, or menstruation, are accompanied by scanty urine, and preceded by a slow or faltering pulse, and when also there is no syphilis or other organic cause to be found to explain their occurrence, I would suggest that they may be due to the effects of uric acid on the circulation in the skull or the action of the heart, and that further investigation or treatment from that point of view is indicated.

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The Indications for Treatment are very much the same as in the case of migraine. An attempt may be made to break through the fits or the stupor and headache which follow them by the use of such drugs as acids, calomel, morphine or the nitrites, with or without temporary compression of the carotid.[1]

I have seen a considerable number of cases where acids did good by relieving the stupor and headache that follow the fits, and in some of these cases the patients used to ask for their dose as soon as they regained consciousness. And it is interesting to remember that a drug which was at one time regarded as a specific for epilepsy, viz., nitrate of silver, acts in exactly the same way as the acids and other drugs mentioned above. Thus in the *Therapeutic Gazette*, 1896, January 15, p. 30, some cases of epilepsy are reported as being cured by nitrate of silver, and it is further remarked that argyria relieves many nervous troubles; but argyria means not only a deposit of silver, but a deposit of urate of silver, just as I have explained in the case of lead in chapter x., and the extensive deposit of urates in the fibrous tissues of the body means, just as in gout (see chapter xv.), that the blood is for a long time relatively clear of urates, hence there is no collæmia to cause epilepsy or other nervous troubles.

The diet treatment must, I think, be very strict, and milk in most cases the only animal food. There must also be no playing with soup, meat extracts, strong tea or coffee, as it is quite useless to cut off meat and allow those things which are worse, and contain no nourishment. When the heart is strong and the fits seem to be due to the effects of high blood pressure on the circulation of the brain, powerful purgation and a rather poor diet may not be bad treatment; but where the heart is weak and the fits seem to be due to its temporary failure before high blood pressure, every care should be taken to reduce the uric acid in the body without unduly reducing urea and nutrition, and it may be well perhaps to try for a time the use of some digitalis which I mentioned above as having been found useful by Dr. S. West. It may be as well also to point out, with regard to diet treatment, that in this disease just as in headache mental depression and chlorosis (see fig. 52) the first effect of a strict diet may be an increase in the frequency and severity of the fits. I mentioned this with a case in illustration in an article on the treatment of these diseases in the Spring and Summer number of *Brain*,

[1] For cases where this was done, see *Lancet*, 1892, vol. i., 858, and vol. ii., 662.

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1897, and pointed out that it was necessary in such cases to guard against discouragement either of patient or doctor, as the temporary increase of the trouble is merely one more proof of its relationship to the excretion of uric acid and collæmia, and shows that the diet has only to be continued to produce relief or cure, and I notice with interest that many recent writers are stating, as the results of their experience, that long-continued treatment by milk diet very frequently diminishes both the number and the severity of the convulsions.

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CHAPTER VIII.

Mental Depression and Fatigue.

Mental depression is a concomitant symptom of the uric acid headache, and I soon found that by influencing the uric acid I could produce or remove it along with the other symptoms (*Practitioner*, November, 1888, paper on "Mental Depression and the Excretion of Uric Acid").

The condition which accompanies the uric acid headache, forming a sort of halo round it, is one of dulness and inability for effort, either mental or bodily, with forgetfulness of names of persons and things. It is closely related on the one hand to sleepiness, and on the other to a mental disposition to take the worst possible view of self and all that concerns it. In this condition self-reliance is absolutely gone, extreme modesty is common or even habitual, a feather weight will crush one to the dust, and even the greatest good fortune will fail to cheer.

If roused from such a condition a considerable amount of irritability and bad temper is sure to be manifested quite out of proportion to the requirements of the case, so that those around a sufferer are soon able to diagnose the condition for themselves.

It seems to me that mental depression is occasioned by a slighter grade of the same condition that produces the uric acid headache, that is to say, a less intense collæmia, or by collæmia associated with debility, or weakness of the heart which prevent the great rise of blood pressure which occasions the headache; while I now rarely or never have enough uric acid to produce a bad headache, I pretty frequently have enough to produce some irritability and mental depression, though this also is slight compared to what it used to be.

On the other hand, clear the blood of uric acid by the use of any of the drugs which produce retention of it, and as the pulse tension is reduced, its rate quickened, and the urine increased, the mental condition alters as if by magic, ideas flash through the brain, everything is remembered, nothing is forgotten, exercise of

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mind and body is a pleasure, the struggle for existence a glory, nothing is too good to happen, the impossible is within reach, and misfortunes slide like water off a duck's back (well-being). To such a terrible extent are we the creatures of the circulation in our brain.

Some have asserted that it is oblivion men seek for when they take opium, cocaine, &c. I believe this to be a great error. Give me an eternity of oblivion, and I would exchange it for one hour with my cerebral circulation quite free from uric acid; and opium or cocaine will free it for me, but as I shall show later on there are other and better ways of obtaining this freedom.

A few years ago (1890), *Punch* gave an extremely interesting illustration of the condition I am here speaking of. I did not note it at the time, and cannot now give the reference, but it was somewhat as follows:—A young or middle aged man is represented reclining in an easy chair in a comfortable or even luxurious sitting room. I think, but I am not quite certain, that the hour is said to be afternoon. On the floor near him is lying a dog, resting or sleeping with half an eye open. *Punch* then goes on to tell that this young man, in spite of his comforts and luxuries, is not happy, and the cause of his misery is the uncomfortable thought which has gradually forced itself into his brain, that his dog does not love him. Presently he rouses himself sufficiently to call his dog with the object of putting to a test the cause of his misery, but the animal rushes towards him and evinces such evident signs of pleasure and affection, that his master is soon compelled to abandon the idea that his dog does not love him. The young man who is thus unable to make himself believe that his dog does not love him is still unhappy, and he rushes in search of a subject to the opposite pole and begins now to worry himself because he does not love his dog. This is more difficult to disprove, and probably the idea lasts him for the rest of the afternoon, but *Punch* intrudes no further upon him.

Now, I have no doubt whatever, that this is drawn from nature, for I have seen many similar cases, and it well illustrates what I want to point out, namely, that the cause of misery is central (the circulation in the brain), but the mind seizes first on one subject and then on another, about which to worry itself. This young man, in exceptionally fortunate circumstances, could find nothing more serious than the mutual affections of himself and his dog, but no doubt he extracted as much misery from these as another man with a similar condition of brain circulation would do from what might appear to others to be more serious troubles. The fact that the cause is central,

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not external, is abundantly proved by the mind wandering to cause after cause as the ones on which it first pitches are shown to be shadows.

"Is life worth living?" That depends on uric acid. The orthodox answer is "that depends on the liver," but as the liver is only one of the sources of uric acid I cannot regard the answer as sufficient.

Soon after I wrote my first paper on mental depression (*Practitioner*, previous reference), Professor Lange, of Copenhagen, kindly wrote to me and sent me a monograph which he published in 1886 on periodical depression and its connection with the uric acid diathesis (*Om Periodische Depressions Zustände, Cobenhavn*, 1886).

His clinical observations and his treatment of the trouble ran parallel to my own, but he knew at that time nothing about the relation of the disturbance of function to collæmia, and merely treated in a general sort of way the uric acid diathesis, which he had found by clinical observation to be related to this periodical depression.

His observations and clinical experience are of great interest as confirming my own, but he had got but a small way into the real pathology of the trouble.

Not long after this, in a review of some of my researches on uric acid, Dr. G. Hofmann (*Prager Med. Woch.*, 1889, No. 28) mentioned, in reference to my assertion that acids cleared the blood of uric acid and produced a condition of mental brilliancy and well-being, that there is a proverb current in some parts of his country of which he speaks as follows: "Es est ganz. merkwurdig dass in Westböhmen, vielleicht auch anderswo das volk den sauren speisen einen gunstigen Einfluss auf die Gemuthsstimmung zuschreibt; wenigstens ist dort das sprichwort, 'saur macht lustig gang und gäbe.'" This is exactly my experience, and acids do it by affecting uric acid; when they fail to affect the uric acid they do not do it.

As before said, blood pressure is directly proportional to the amount of uric acid circulating in the blood, but blood pressure means, and is due to, obstruction of capillaries; therefore obstruction of capillaries is proportional to the amount of uric acid in the blood.

But obstruction of the capillaries in the brain means, probably, stasis and hyperæmia of the brain. Therefore, *cæteris paribus*, stasis and hyperæmia of the brain are proportional to the uric acid in the blood.

Now, it is well known that in mental activity and excitement the brain is large and its cortex hyperæmic, and under opposite

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conditions it is relatively small and anæmic. It is also anæmic in sleep.

With regard to this point, Dr. S. G. Burnett, in a lecture on "The Diagnosis of Incipient Melancholia" (*New York Medical Journal*, May, 1891, p. 497) says: "In melancholia there is a dejected and subdued appearance with decreased activity of mind and body, slow defective mental reflexes, and a delirium of self-reproach and persecution. Meynert believes the symptoms found in melancholia are the result of an anæmic condition of the cerebral cortex. Clinically we know that an abnormally anæmic condition of any organ means starvation, followed by a decrease and change in function, and if continued long enough the condition must become degenerative in character." And with regard to these remarks about anæmia and hyperæmia, it seems probable that stasis and hyperæmia effect, in exactly the same way as anæmia does, the interchanges between the blood and the tissues of the brain, hence their effects are similar or identical.

Among the symptoms of incipient melancholia the writer just quoted lays great stress upon pain in the back of the neck (neuchalalgia), insomnia and mental depression when occurring together. From this description of neuchalalgia it seems to be identical with my uric acid headache, which, when very severe, is right in the centre of the occiput, just above the insertion of the ligamentum nuchæ, and about insomnia accompanied by high tension Sir W. H. Broadbent and others have written.

It seems probable that when insomnia is associated with high blood pressure the cerebral arteries are distended by the high pressure, just as the arteriometer shows the radial artery to be distended under similar conditions, and are unable to shut off the blood to the extent required to produce the anæmia of sleep; but the moment the pressure is reduced by a drug like calomel, sleep supervenes at once, and this effect is often so marked that it may be difficult to persuade patients that they have not been given a dose of opium, and indeed the soporific effects of opium may be due at least in part to its power of lowering blood pressure. It is also a point of interest with regard to collæmic sufferers from insomnia that their most common complaint is not that they do not get to sleep in the p.m. hours when the collæmia is slight, but that they wake up in the early a.m. hours, when, as we have seen, the collæmia is most likely to be severe, and cannot again get to sleep, and in my experience the proper diet treatment of collæmia has in such cases been most successful.

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The great point about the mental depression due to uric acid is, as rightly insisted on by Professor Lange, that it is periodical, in which it resembles the uric acid headache and the fits that are due to the same cause. Where depression is chronic and continuous, with but little fluctuation, it is more probably due to morbus cordis or other organic cause, than to uric acid, though, as I said just now, uric acid may intensify the effects of organic disease.

We have then a condition of mental depression, between which and melancholia with delusions I agree with Sir W. H. Broadbent in believing that there is no absolute line of demarcation (see Croonian Lectures, 1887), and this depression is due to a certain amount of stasis and hyperæmia in the brain, brought about by the high blood pressure which an excess of uric acid in the blood (collæmia) produces. If this is the case the depression in question should bear just the same relation to the excretion of uric acid as the other diseases of which I have spoken, and a great many factors that influence uric acid should alter in one way or another the depression it causes.

In physiological conditions we have seen reason to believe that there is more uric acid in the urine, and more in the blood in the alkaline tides of the day than at night, that the excretion of uric acid is relatively greater in the summer than in the winter, and that consequently there is more in the blood in the former than in the latter (see figs. 3 and 4).

Therefore, mental depression that is due to uric acid should be worse in the morning hours of each day, and should also be worse in the spring and summer. A good many sufferers are also distinctly worse in the hours of the afternoon alkaline tide, just about afternoon tea time; and a fact of considerable interest in this connection was brought to my notice by an intelligent patient, who found that if he took a cold bath in the morning his afternoon depression was always worse than if he took a warm bath. Now, it is obvious that if the cold bath and the exertion of taking it acted as stimulants to his nutrition, causing a rise of urea and acidity, they would diminish for a time the excretion of uric acid in the morning, and the amount so held back would most probably pass through the blood in the afternoon alkaline tide, just as in the artificial headache which we produced in chapter vi., and account for the observed increase of depression; a warm bath on the other hand would increase the excretion in the morning and leave less for the afternoon, and in exactly the same way some exercise with perspiration in the early morning hours will increase the quantity of uric

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acid excreted in those hours (see fig. 39), and then there will be but little left to be excreted in the afternoon, and well-being may take the place of the usual depression.

In my first paper in the *Practitioner*, I remarked on the fact that in France the suicides in July far outnumber those in any other month, and suggested that the effect of season on the excretion of uric acid might give us a simple explanation of the fact, and I see that some French statistics quoted in the *Lancet*, 1893, vol. i., p. 1413, show that of all suicides 31 per cent. occur in spring, 26 per cent. in summer, 21 per cent. in autumn, and 22 per per cent. in winter; probably the autumn, the first cold after the plus excretion in the summer, furnishes the lowest urate excretion of the year, just as spring, the first warmth after the retention of the cold season, furnishes the largest urate excretion of the year, as we see to be the case in fig. 4. I am also inclined to believe, and have collected some records of cases bearing on the point, that the fatal act is more often committed in those hours of the day when the excretion of uric acid and the contemporaneous collæmia are greatest.

Thanks to the kindness of a friend I was able to obtain cuttings of all the cases of suicide in the daily and weekly papers for about twenty days at the end of March and beginning of April of 1894.

The total number of cases thus tabulated was 99, but of these four were recorded so indefinitely that nothing could be said as to the hour.

Of the remaining 95 cases, in 66 the hour was definitely stated, but in 29 it was only given as morning, afternoon, evening or night.

Now, on dividing the 24 hours into two parts, from 5 a.m. to 5 p.m., and from 5 p.m. to 5 a.m., we get probably the largest excretion of uric acid in the 12 hours, 5 a.m. to 5 p.m., and the smallest excretion in the 12 hours, 5 p.m. to 5 a.m. (see figs. 1, 2 and 3).

And now taking the 66 cases in which the hour at which the fatal act was committed is definitely stated, we get in the 12 hours, 5 a.m. to 5 p.m. 37, and in the other 12 hours 29 cases.

Of the 29 less definitely stated cases, 14 were in the morning, 9 in the afternoon, 5 in the evening and 1 in the night, and here again we see a preponderance of alkaline tide hours.

And I should not expect any more than a preponderance in the normal collæmia hours, because we are here comparing pathology with physiology, and though, as explained in the case of uric acid headache, the pain will probably be at its worst in the alkaline tide

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hours, once digestion has been completely upset the plus excretion and collæmia may go on almost continuously through the 24 hours.

Among a few other cases collected by myself from the daily or weekly papers I usually read, I find the following suggestive notes: one was a case of a woman in labour, several had poor health, and in one this appeared to be due to previous influenza; another suffered from sleeplessness, and little things caused much trouble; another had been depressed in spirits; another had had hemiplegia, and suffered from low spirits; and we have in these, I think, very clear evidence of the presence of collæmia with high blood pressure and its results.

Some extremely interesting facts bearing on these points have appeared from time to time in the medical papers; thus in the *Lancet* of July 28, 1894, the Paris correspondent gives notes of an epidemic of suicide then occurring in France, in which he points out, among other things, that the epidemic coincides with the onset of hot weather, and that the fatal act appears to be most often committed between the hours of 6 a.m. and 12 noon.

In a letter to the *Lancet*, August 11, 1894, on these points I showed that gout which corresponds with retention of uric acid and its absence from the blood, affects exactly the opposite poles, both of the day and of the year, being at its worst in the evening hours and at its best in the morning hours, and on the authority of Sydenham, worst in February, and best in the warm summer months.

And the *Lancet* of August 17, 1895, has an annotation on this subject, in which they refer to my letter above mentioned, and acknowledge that my suggestions as to causation are helpful; but they end with the conclusion that suicide is due to moral failure, and is not to any great extent connected with physical conditions, such as collæmia and its effects on the circulation.

This is a conclusion which appears to me to be absolutely wrong and false, and also against the weight of evidence.

For there is no boundary line between those who suffer from the mental depression of collæmia and those who have well-marked melancholia from the same cause; in nature we meet with all gradations of cases, from the one to the other.

Of my own experience of mental depression I can say this, that it is so insidious in its onset and course that even knowing what I do about the action of collæmia in producing it, I have often great difficulty in persuading myself that things are not really all wrong, and that a dose of calomel will make them seem bright again; and if I am deceived, how much more will those be so who know nothing

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about the physical causation of these troubles; and the quotations given above about cases of suicide show that to onlookers, the troubles that weighed down to the ground the unhappy collæmics were small matters or trifles.

To the mentally depressed, however, this is far from being the case; they are terrible realities surrounded by the inky blackness of despair.

Then, again, as to moral sense, thought and resolution, I have no hesitation in affirming that in these conditions they have just no power at all; in the terrible darkness of mental depression the stars of hope, faith and trust are blotted out, and give no gleam of light whatever.

In this condition a man cannot think of the name of his dearest friend, or the verse of his best loved poet, logic is nowhere and even simple arithmetic is impossible—in a word, he is, just as the jury say, temporarily insane, and differs only in degree, but not in kind, from the man whom we send to an asylum under certificates. The one we hold morally irresponsible, the other, according to the *Lancet*, is not so, but I feel sure that greater and truer knowledge will oblige us to take a different view.

Then, again, in the *British Medical Journal*, 1895, vol. i., p. 378, it is pointed out in an interesting leader that suicides are most frequent between the ages of 45 and 55, and this, I would remark, is exactly the age at which the metabolism and nutrition of the body begin to slacken, and thus the uric acid stored up in previous years begins to pass through the blood; these also, if I mistake not, are just the years in which we begin to get troubles with high blood pressure and its results—sleeplessness, mental depression, causeless worry, chronic Bright's disease, and cerebral hæmorrhage.

To hold that such people are responsible for their actions is to do them a cruel injustice, and to try to deter them from their rash act by moral suasion, is like a child's attempt to stop the rising tide with a bank of sand.

The *Lancet* says (previous ref.), "Where they are free to operate the reserves of moral sense, thought and resolution have either been previously exhausted, or have not been drawn upon."

My point is that under the conditions of circulation and nutrition that are present in the brain in a case of well-marked mental depression they never are "free to operate."

Those who for days, weeks, months or years before the fatal act, were sleepless, depressed, worried about trifles, had chronic Bright's disease, or cerebral hæmorrhage, were suffering from well-marked

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disease, and should have been treated with suitable remedies other than mental or moral, and, indeed, I believe that dyspepsia alone has caused far more suicides than all the moral depravity in the world, and I would sooner believe that there is no such thing as moral depravity apart from bodily disease, than that suicide can be due to moral depravity alone, when structure and function are perfect. The fact now brought forward that suicide shows marked fluctuations corresponding with the daily and yearly fluctuations in the excretion of uric acid, proves that it is intimately connected with collæmia; it also fortunately points the way to a fairly certain means of prevention.

Again, it has appeared to me that the irritability and bad temper of collæmia, due to the stasis and hyperæmia it brings about, may account for a certain number of murders, and they also have been noticed to have a seasonal variation. Thus May has been called the month of suicides and murders (*Lancet*, 1890, vol. i., p. 1,208).

May is one of the first months in which we have any decided warmth, and with the falling acidity some of the uric acid held back and stored in the winter begins to be dissolved in the blood, and more or less marked collæmia results.

In a word, I believe that the above-mentioned physiological fluctuation in the excretion of uric acid, and the concomitant collæmia completely account for the observed fluctuations in the incidence of mental depression, suicide and murder. Then, again, in the *British Medical Journal*, 1897, vol. i., page 392, there is the record of a case in which stupor cleared up completely on the supervention of a little febrile movement, and this is regarded by the observer as curious, but if we bear in mind that fever cures collæmia, acting probably both by raising the temperature and diminishing the alkalinity of the blood stream, there is nothing curious about it.

As regards experimental results, I have said that I can produce or remove this mental depression at any time, just as I can produce or remove the uric acid headache and the slow high tension pulse which accompanies both.

Alkalies will produce it, provided there is some uric acid in store for them to act upon, and acids, opium, cocaine, mercury, iron, zinc, strychnia, &c., will remove it. I have very little doubt that the use of alcohol, opium and cocaine to remove the uric acid collæmia and its cerebral effects, has often led to their abuse, for they cure present depression by driving the uric acid out of the blood into the liver, spleen, joints, &c., where it is stored up, but the next time the acidity falls, generally in the alkaline tide of the following

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day, out it comes again into the blood, and collæmia worse than before is produced. From this secondary collæmia of what I have spoken of as the rebound, there is, so far as the indulger in opium or cocaine knows, no escape except by repeating the dose, and so he goes on and on, ever accumulating more and more uric acid, and requiring continually larger and larger doses of the drug to keep it out of the blood, and this is the beginning of chronic morphinism.

In my own personal experience I soon got over this difficulty by removing the uric acid from the body. Supposing that I suffer from mental depression I can remove it by a dose of morphine, say gr. ¼, and then I follow this by several xv. gr. doses of salicylate of soda, which, as we have seen, eliminates uric acid best when the acidity is high, and further prevents it from affecting the capillaries to any great extent as it passes through the blood, just as alkalies may do when there is no great excess of urate in the body.

The uric acid, held back by the morphine, is thus eliminated by the salicylate; there is, therefore, no collæmia next morning, and no necessity to take another dose of morphine.

This experience has led me to suggest the use of salicylates in the attempt to break through the morphine habit (see p. 55).

As regards alcohol, I was much interested to hear it said at a dinner given by the Vegetarian Society of London a few years ago that the adoption of a vegetarian diet was one of the best means of overcoming the craving for drink, for if this craving is in any way due to the mental conditions of discomfort produced by the circulatory disturbances of uric acid, this is just what I should expect.

Like morphine, cocaine, and alcohol, of which we have been speaking, meat itself is a stimulant, and this is the real cause of the difficulty which so many experience in giving it up. As regards nutrition there is no difficulty, for plenty of things can be found which will nourish the body quite as well or better than meat. Now meat acts as a stimulant in exactly the same way that morphine, cocaine and alcohol do so, by clearing the blood of uric acid. The uric acid, xanthins and salts it contains diminish the alkalinity of the blood, and for a time keep it clear of uric acid, but as in the case of the drugs this is followed by a rebound, and then more meat or alcohol, morphine or cocaine in its place must be taken to prevent the resulting depression, and the use of one stimulant leads to that of another, and the more they are used the more uric acid will be retained, and the more they will have to be used in ever-increasing quantities to hold it back. At last a time arrives when further stimulation is impossible; and then there is an enormous rush of uric acid

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through the blood, with headache, melancholia, or uræmia as its result. Thus I have been told by a patient of mine whose daughter, among other good works, has a Home for Inebriate Women, that her own experience has taught her that flesh diet is the very worst for them, and she does what she can to tempt them away from meat, but she says: "you can really see joy in their faces if a large joint of meat is brought in," just, I remark, as you would see joy in their faces if a keg of whiskey was placed on the table. I also hear from the same source that if the craving for alcohol is overcome that for meat goes also. It is stimulation that is wanted, not nutrition.

I would also point out that meat not only produces in this way a craving for stimulants to overcome the rebound from its own stimulation; but it also produces thirst, so that those who use it are driven to drink very considerable quantities of such fluids as beer, and thus introduce ever more and more of the stimulating acids and alcohol.

Now just as meat produces thirst by freeing the capillaries and allowing water to run out of the blood (see previous remarks about fig. 3), the alkaline salts of fruits and vegetables not only prevent such great freedom of capillaries and running off of water, but the fruits themselves also introduce into the body a considerable quantity of water. For these two reasons, those who eat fruit have but little thirst as compared with those who eat meat, and we can now see clearly why a non meat diet is one of the best means of overcoming a craving for drink; but for an excess of meat it would probably never have originated at all. Meat will in this way also produce constipation by diminishing the water available for the fæces, and meat eaters are always constipated (see as to importance of sufficient water in preventing constipation, Dr. T. Lauder Brunton, *Lancet*, 1896, vol. i., p. 1413).

No doubt those who eat no meat have no stimulation, and the stimulation by meat or drugs is pleasant while it lasts; but this is far more than counterbalanced by the terrible depression that follows, and which, when too late, its victims make violent endeavours to escape from.

But those who have no ups have no downs, and so long as their blood is kept pretty steadily free from uric acid, their general level of function and nutrition is considerably higher than that of those who go in for constantly repeated stimulation and think it strength.

As we shall see later on, the cerealeans and frugivora among mankind have both greater muscular energy and power of endurance than the carnivora, and we shall see why they have it, though meat

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eaters would fain persuade us that it is all the other way. No doubt all stimulation is wrong, and we thus merely enjoy to-day by mortgaging to-morrow; and just as we may rise to-day a few inches above our normal level so shall we fall to-morrow exactly the same amount below it; those who live on a uric acid free diet can alone have a steady high level of function every day, and these never feel the want of any stimulation.

For my part, and as one of the results of this research, I am inclined to believe that mankind are trying to make themselves carnivora, when nature intended them for frugivora, and that they will presently wake up to the fact that they are even now paying an enormous price in the shape of mental and bodily disease for their follies.

As regards the production of well-being, the acids mixed with the alcohol are probably more efficient than the spirit itself, but the alcohol, in so far as it acts as a stimulant, would probably raise the acidity, free the capillaries, and produce some well-being: on the other hand, we know that whiskey has comparatively little gout producing powers—hence the freedom of the Scotch—while acid beer and wines are much more powerful gout producers, though containing less alcohol; and the beverages that produce gout will be the most powerful preventives of collæmia, though any or all of them will relieve for a time mental depression and similar feelings (see figs. 54 and 58).

In pathology the conditions which produce mental depression are just those which bring about collæmia, such as loss of employment and deficient food, functional or organic disease interfering with digestion and nutrition; anything that diminishes nitrogenous metabolism and the excretion of urea, as the acidity falls with the urea. A man while in good work eats freely of meat and drinks 4d. ale; as a result his acidity rules high, hence he excretes uric acid in relation to urea of 1—40 or 1—50; that is, the excretion of uric acid falls short of formation and introduction, and he daily stores or retains a certain quantity in his body. Now come bad times—he is out of work, can afford no beer, and only little meat; down goes urea and acidity, and the uric acid he has previously retained at once begins to pass into the blood and urine; there is collæmia with slow high tension pulse and mental depression, and his wife tells you he is fretting because he has no work; but clear the uric acid out of his blood, and he will cease to fret though he still has no work.

Then again, most fevers, especially short sharp fevers, such as influenza, pneumonia, scarlet fever, erysipelas, produce the material for more or less intense collæmia.

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It is well known that fevers raise the acidity of the urine, and I have mentioned on p. 35 a good instance of this recorded by Sir W. Roberts. Pieper also has shown that all fevers diminish the alkalinity of the blood except such as are complicated by dyspnœa and cyanosis. I have suggested (see p. 83) that in fevers there is increased oxidation which produces both increased formation of heat and increased formation of acids, but where there is dyspnœa or cyanosis oxygen is deficient, and then neither does the temperature rise so high nor the acidity increase so much as in fevers not thus complicated.

But be this as it may, fever generally entails a rise of acidity, and this produces a deficient excretion of uric acid and accumulates a store of it in the body; when the fever comes to an end acidity falls, and then the uric acid is dissolved out and collæmia results.

Such collæmia will be proportional to the amount of uric acid that was retained by the fever, and it may be reinforced by any uric acid that had been previously stored in the body, or that was introduced during the fever by a more generous than wise use of beef tea and meat extracts. Hence, in the convalescence of acute fevers there is sure to be more or less collæmia, which will continue till the stores of uric acid have been all swept out, or till the acidity again rises with improving nutrition; till one of these things happens there will be daily collæmia with slow high tension pulse and mental depression; this is no doubt the cause of the slow high tension pulse so often seen during the first few days after the crisis of a pneumonia and other fevers—a condition described by Riegel (*Zeits. fur Klin. Med.*, 1890), and others as post febrile bradycardia (see p. 173).

I have very little doubt that the increase of suicide in this and other countries that followed our recent epidemics of influenza (see *Lancet*, 1894, vol. ii., p. 445) was due to such post febrile collæmia, and that this was increased by the treatment of influenza as a depressing disease, with a free allowance of wine and beef tea throughout.

I have also mentioned two cases of pneumonia that were under my care about the same time: one was a strong and powerful man, the other a weak and ill-nourished woman; in the former the post febrile conditions, including bradycardia, were very prominent, in the latter very slight, and the difference was simply due to the fact that the big man with his large metabolism of nitrogen stored much urate at the time of the fever, while the ill-nourished woman stored but little, and the post febrile symptoms were proportional in each case to the amount of urate passing through the blood (post febrile collæmia).

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This man also presented another symptom of great interest, for during the fever of his pneumonia he had no albuminuria, but on the first day of subnormal temperature, when the symptoms of collæmia were very marked, he had a trace of albumen in his urine. I have no doubt that this albuminuria had an identical causation with that which accompanies migraine or epilepsy, or with paroxysmal hæmoglobinuria, from which it differs merely in degree, and I believe that an albuminuria similarly produced occurs in the post febrile period of not a few acute diseases; and that if the post febrile collæmia is severe and prolonged it may pass on into actual Bright's disease, with which it is identical in causation. And this we do see actually occurring after some cases of scarlet fever, and we shall also see further on (chapter xiii.) that the use of salicylates during the fever, which would, no doubt, eliminate much of the uric acid and so prevent post febrile collæmia, has been thought by some to prevent the subsequent onset of albuminuria and Bright's disease (see further on the facts about fatigue, and the effects of uric acid on the formation and excretion of urea, and the arguments in chapters xii. and xiii.).

Bright's disease again is frequently associated with suicide, and in Bright's disease there is chronic collæmia, with obstructed capillaries and slow high tension pulse.

Menstruation should probably have been mentioned under physiology, but in menstruation there is very often collæmia, because this condition is commonly accompanied with some disturbance of digestion, failure of nutrition, and fall of acidity (see figs. 30 and 31). I have already (chapters vi. and vii.) pointed out that women who have fits or the uric acid headache nearly always suffer from attacks at the catamenial period. Sir W. H. Broadbent has remarked that the pulse is often slow and of high tension in menstruation, and Dr. Barnes (*Brit. Med. Journ.*, 1890, vol. i., p. 1401) has pointed out that museums can easily be stocked with the organs of menstruating women in consequence of the fact that they so often commit suicide at this time, and we have here again most convincing proof of the connection between suicide and collæmia.

It seems to me that at this point we are on the borders of a very wide field in psychology which we may presently be able to cultivate to some purpose; and the question presents itself, how far is the bias of women towards religion, and generally to take serious views on matters which men often regard lightly, how far is this due to the more or less continued effects of uric acid on their arterial tension and cerebral circulation? In attempting to answer

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this question we must bear in mind, as I have said, that depression breeds depression, that once there is an excess of uric acid in the blood this continually tends to depress more and more both metabolism and nutrition and keep them down. In a woman who is strong, active, and well nourished the collæmia of the menstrual period will be quickly put an end to by the rising acidity of an active nutrition; but in one who is weak and ill nourished acidity may remain depressed for days or even weeks, she will suffer from chronic collæmia, for the depression of one period will hardly have passed off before the next is due, and its paralysing effects on the activity of mind and body may suffice to give a bias to her whole life; such a woman meets with a disappointment and has not power to throw it off; she mopes and nutrition suffers, and collæmia becomes established with mental depression; she goes in for some morbid religious extravagance, and perhaps ends in a convent. This is an extreme case, but I believe the general bias of the female mind is often determined by similar factors.

In this connection I was much interested to see an article in the *Brit. Med. Journ.*, 1893, vol. ii., p. 258, in which it was said that judging from the advertisements in religious papers the disorders from which their readers most frequently suffered, were "fits and deep depression."

I must now leave my readers to decide for themselves how far the fits and the deep depression, and the morbid religious bias as well, and I am speaking of morbid and not of natural religious feeling, are due to uric acid and its effects on the intracranial circulation; but we all know that there are conditions associated with feeble or failing nutrition and probably collæmia in which "the devil a saint would be."

In several papers also I have mentioned the experiments of Drs. Roy and Sherrington, which show that injection of acids into the veins produces enlargement and hyperæmia of the brain (*Journal of Physiology*, vol. xi., p. 85), and have suggested that the acids really affected the vessels and brain circulation indirectly by their action on uric acid.

Roy and Sherrington found on the other hand that alkalies diminished the blood in and reduced the volume of the brain; and here we have, I think, actually demonstrated the effects which I can produce on the circulation of the brain, and so on the mental condition by influencing uric acid.

By giving alkalies I can produce collæmia with slow high tension pulse, obstructed capillaries in the skin and kidneys, stasis and

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hyperæmia of the brain and mental depression; on the other hand by giving acids I can free the blood from uric acid, free the capillaries, cause a good circulation in the brain, and mental brightness and well-being.

If it is objected that the action of the acid in these experiments is too quick for it to have acted indirectly on uric acid, I should reply that in chemistry a precipitate occurs the moment a precipitant is added to a solution, and I fail to see why it should be delayed in the blood in which the action is probably very similar. And in Mr. Saul's experiments, previously referred to, colloid uric acid is at once thrown down when the solution is acidified. Well-marked effects on the circulation can be produced in a few minutes by means of drugs taken by the mouth, and I see nothing to wonder at if the same drugs produce effects in a few seconds when directly injected; nor is there, I think, anything here to make us believe that an acid acts directly on the vessels when it is injected, and indirectly on uric acid when it is swallowed producing the same results in both cases.

Roy and Sherrington further point out that the intravenous injection of opium produced but little effect on the circulation of the brain, and yet when it is swallowed by man it is easy to show that it has a most powerful effect on the capillary circulation of the whole body, and also on the mental condition. How do they explain such different effects in the case of opium, while acids have much the same effect whether injected or swallowed? From the point of view of the uric acid causation of these vascular effects the matter is simple enough, for opium has no direct effect on the solubility of uric acid, in which it differs from acids and alkalies.

Now, the indirect effect of opium is, as I have pointed out (*Brit. Med. Jour.*, 1889, vol. ii.), probably entirely due to its effects on the peristalsis of the intestines. By slowing down peristalsis and the passage of the contents of the large intestine, it promotes the absorption of acid fluids from that part of the alimentary canal, and thus raises the acidity of the urine and diminishes the alkalinity of the blood. But if from any cause it fails to check peristalsis and raise the acidity of the urine, it also fails to affect the capillary circulation of the body, and will then produce neither mental well-being nor absence of fatigue. It is interesting also to remember that belladonna (fig. 9), which has an effect on the intestines almost exactly the opposite of that produced by opium has also the opposite effect on the solubility of uric acid, and so on the nutrition and function of the body.

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Now, opium may fail to raise the acidity of the urine from several causes, such as the presence of much alkali in the food, or in conditions where there is dyspepsia with vomiting and diarrhœa, which it has to overcome before it can do anything to raise the acidity.

For this reason I believe that opium has less power, dose for dose, over the vegetarian native of India, than over the meat-eating native of these islands, and its action in myself is certainly far less powerful now that I am almost a vegetarian, compared with what it was some years ago when I ate ordinary diet.

Had this not been so I should have given curves showing the effects of opium on fatigue, and the excretion of urea, but to do this I found that rather large doses of opium would have been required, and I therefore resorted to calomel which acts directly on uric acid, and is independent of acidity (see fig. 41).

Small doses of opium do not raise the acidity of my urine to any marked extent, and they do not therefore clear the blood of uric acid or cause well-being and absence of fatigue, except to an extent which is insufficient to show well in curves; but there is no doubt that opium, cocaine and other drugs which are so well known to diminish or prevent fatigue, act just as calomel does by clearing the blood of uric acid, so that the vessels are free to relax, and there is consequently a good circulation through the muscles with prompt elimination of urea and active metabolism; but when, as in my case, they fail for the reasons given above to affect the solubility of uric acid to any marked extent, they also fail to a corresponding extent to affect fatigue and the excretion of urea. If it is urged that acids relax and alkalies astringe the capillaries directly, I should reply that in the human subject if you remove all the available uric acid, alkalies will fail to raise arterial tension, because they fail to produce collæmia. Again, lithia markedly diminishes the acidity of the urine, but yet it quite fails to produce either mental depression or scanty urine, on the contrary, it causes well-being and diuresis (see pp. 52 and 162), and the excretion of uric acid tells us why it does so, for in place of producing collæmia as soda and potash do, it clears it out of the blood and diminishes its excretion.

Again, lead and iron and a number of other metals produce retention of uric acid, and while this action lasts they produce also unobstructed capillaries, well-being and diuresis. Everything that clears the blood of uric acid causes diuresis if there is available water in the blood; and conversely almost every diuretic in the pharmacopœia and out of it, is found on investigation to clear the blood and urine of uric acid, and in physiology also, as we have

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seen, water and uric acid go in opposite directions. I have shown that all these substances produce the same effects on uric acid; from the other point of view it would have to be shown that they all separately produced the same effects on the arterioles or capillaries.

Then again, I have pointed out that the headache, slow high tension pulse, depression, and other symptoms of collæmia are proportional in every way to the excess of uric acid in the blood and urine, but bear no relation whatever to the amount of alkali which may have been used to produce them artificially.

In a word, all the phenomena are proportional to the uric acid, but not to the drugs which only act indirectly upon it.

And my experience of the effects of diet in my own case (though it by no means stands alone) are amply sufficient to prove this, for if alkalies contract the arterioles of the brain and produce anæmia and depression, headache, &c., I ought to be much worse now on a milk and farinaceous diet, which has greatly diminished the acidity of my urine, but on the contrary I am much better now and have not a tenth part of the headache, high tension pulse, and depression I used to have on an ordinary meat diet, and I am glad to be able to say that many of my patients have had similar experience. Severe collæmia is now impossible, hence its effects fail to appear, but alkalies are plentiful in the circulation, and have no effect on the arterioles.

And my experience has convinced me that the best way to keep the brain circulation free from uric acid is not to dose it with opium or cocaine, which, while clearing the blood to-day, store up the poison for future trouble, but to reduce the formation and introduction of uric acid, and to provide for its constant free excretion by a plentiful supply of alkali in the shape of fresh fruits and vegetables, and in winter also it is necessary to clothe fairly warmly and otherwise to guard against the too prolonged action of cold, as this tends to raise acidity and cause retention of urates, especially when its action is aided by a diet relatively poor in fresh fruits and vegetables (see remarks on fig. 65).

I am here speaking of functional, temporary, periodical depression, though I quite believe that if the vascular conditions that produce it are very often repeated over long periods they may at last bring about some organic changes which are irremediable and cannot be removed. I have, nevertheless, been able to effect great improvement in depression, which had lasted on and off through very many years by such alterations in diet as I have mentioned.

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There is probably no fact that is more widely recognised in this portion of the globe, than that mental irritability and depression are relieved by the smoking of tobacco, and if we look up tobacco in a system of therapeutics we find that it is classed with the depressomotors, *i.e.*, with the drugs that diminish muscular power and enfeeble the heart, and among drugs having a similar action it is interesting to note that ipecacuan and antimony have a similar power in relieving migraine.

It has apparently been pointed out by several observers that smoking tobacco diminishes intellectual power (see letter by Dr. C. R. Drysdale in the *British Medical Journal*, 1896, vol. ii., p. 238, and references there given), and if it does in any way weaken the power of the heart it is easy to see how it may hinder the due nutrition and development of the brain. I am also indebted to Dr. Morgan Dockrell for the information that tobacco may precipitate alopecia senilis; but that the hair may recover if smoking is given up, so that it apparently affects nutrition on both sides of the skull.

My observations on the effects of tobacco smoking on the pulse seem to show that it lowers arterial tension, and quickens the rate of the heart's action, and it is easy to understand that in accordance with Grashey's observations[1] (see p. 200) it will in this way increase the volume of blood passing through the brain, and so produce well-being; and this well-being produced by tobacco is not accompanied by a desire for activity and a feeling of tone in the muscles, but rather by slight languor and disinclination for exertion.

The arteriometer also records the effects of tobacco smoking, as on several occasions I have found a distinct diminution of the diameter of the radial artery after smoking for 30—40 minutes. I think also that we must not lose sight of the fact that quite apart from the action of nicotine or tobacco when directly absorbed, the inhaling of the products of combustion of any vegetable matter means the taking in of a certain amount of the acid products of combustion, such as nitrous or sulphurous acids, which may be absorbed from the mouth and nose in sufficient quantity to affect the alkalinity of the blood; so that tobacco is another instance of a substance which ministers to man's comfort like opium and cocaine by clearing his blood of uric acid, but like these also, its first action may be followed by a rebound with irritability, mental depression, and tendency to suicide (see *British Medical Journal*, 1890, vol. ii., p. 1161.)

Having taken the view that, in accordance with the above facts,

[1] *Fest-Schrift Munchen* (J. F. Lehmann, 1892).

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mental depression bears exactly the same relation to the excretion o urates that headache does, and that the causation of the one differs from the causation of the other merely in degree, I was much interested to be told by one of my patients (a man of conspicuous mental ability, who had all his life suffered from mental depression), that when he had his worst attacks, which were always in the early hours of the morning, he was accustomed to obtain relief by sitting upright in bed, in exactly the position that I have to assume in my headache; and the fact is not only interesting as a parallel, but it proves, I think, that in this case the mental depression was not due either to feeble heart or to cerebral anæmia.

I do not doubt that mental depression may be due to a weak heart, and consequent cerebral anæmia, but such depression would pay little or no attention to fluctuations in urate excretion, and would be benefited rather by lying down than by sitting up.

It is interesting also to remember that in mental depression associated with high blood pressure, digitalis does harm. I have several times given it in cases where there seemed to be a doubt as to the power of the heart, and have seen cases where others have done the same, and the only result was to make the depression worse.

One can easily understand why this should be so, as digitalis affects both factors in the causation of high blood pressure: it strengthens the heart and contracts the arterioles. On the other hand, where mental depression is associated with real cardiac weakness and low tension, digitalis may do a great deal of good.

The relation of these depression attacks to the early morning hours and the similar relation of melancholia to these hours (see "Proceedings of the Medical Society of the State of Pennsylvania," June, 1890), are of great interest in connection with the large excretion of urates and scanty urine, which characterise these same hours in physiological conditions, and I look upon the pathological condition as a mere exaggeration of the physiological (see figs. 1, 2 and 3).

An extremely interesting case illustrating some of these points is published by Dr. Willoughby Gardner in the *Lancet* (1891, vol. i., p. 1311), and with regard to this I think it is not too much to say that I can explain completely every symptom he mentions, and if a case had been manufactured to suit my theories it could not have been better done.

A patient suffers from gout attacks and gouty dyspepsia. On March 3, 1891, he has acute gout in the left foot. From this he recovers two or three days later, considers himself well, and proposes to return to work.

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On Sunday, March 8, he attended three long religious services and took no exercise. On the morning of March 9 he was suffering from acute melancholia of a religious type, with delusions and threats of suicide. Pulse weak, but artery full between beats. Heart, second sound in second right intercostal space loud and ringing.

He was given a mercurial purge and mustard blister to nape of neck.

In the middle of the night he was seized with a slight attack of gout in the left foot (the same foot as before, I remark), and "at once all depression completely disappeared," the pulse felt stronger, and the radial artery could not be felt between the beats, the second sound of heart no longer accentuated or loud.

The case in terms of uric acid causation would read as follows:—Gout, alternating with dyspepsia, cure of an acute attack of gout, some dypepsia, and collæmia. While this is going on he sits out three long services in a cold church, and takes little exercise. This produces minus skin activity, a rise of acidity, and some retention of uric acid. Next morning, in the alkaline tide, the collæmia returns reinforced by the amount retained on the Sunday. This obstructs the capillaries and raises blood pressure, and this in turn produces such an altered circulation in the brain that melancholia with delusions results.

A mercurial purge is given, this clears the blood of uric acid, driving it into the liver, spleen, and joints, especially its old friend of previous attacks, the left foot, and produces a gout attack in the night, and at the same moment, the blood being cleared of uric acid, the pulse alters its character, the melancholia due to the effects of high blood pressure on the cerebral circulation clears up completely. Mercury here acts just as a dose of iron, lead or even lithia would have done, and for the same reason, for urate of mercury like calomel and other salts, is very insoluble, so that the urate of mercury tends to be deposited especially in those joints where previous attacks had left some urate to attract it.

It would be difficult to find a case which more completely illustrates my main points than that narrated by Dr. Gardner.

I should be quite ready in such a case to undertake to produce either gout or melancholia to order, and in other cases similar effects can be produced proportional to the amount of urate that is in hand, and can be acted on.

While these facts are before us it is not difficult to see why an attack of fever should restore mental health in melancholia, or why thyroid extract should be used to produce the same result (see *British Medical Journal*, 1895, vol. ii., p. 765).

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So far we have been talking of depression or fatigue of mind, but I believe that fatigue of body has a similar if not identical causation. If, as we know well, bodily strength and power of endurance are increased by drugs like opium and cocaine, which produce a free circulation and metabolism in the nerve centres and in the muscles, then obviously the conditions which hinder the circulation and diminish the metabolism in these important structures will produce fatigue of body as well as depression of mind.

As a good deal has been written on this subject lately, it may be of interest to go into it further, and it will form also a prelude to what I shall have to say about the more important effects of uric acid on metabolism and nutrition in future chapters.

Now I pointed out about nine years ago[1] the fact that the fall of uric acid excretion brought about by the administration of an acid was almost always accompanied by a rise in the excretion of urea.

But owing to ignorance in other directions and to what I now regard as the erroneous observations of others I gave what was probably a wrong explanation of the fact, and otherwise failed completely to appreciate the importance of my observation.

Since that time I have found out that uric acid taken by mouth is not converted into urea, but is in due time excreted as uric acid in the urine[2] (see figs. 23 to 29).

And also that while a marked fall in uric acid is commonly accompanied by a rise of urea, a marked rise of uric acid is also commonly accompanied by a fall of urea.

It was only, however, comparatively recently in working at the physiology and pathology of fatigue that I appreciated something of the real bearing and importance of my previous observations.

As we shall see and as I pointed out in previous editions, the effect of exercise is to lower the acidity of the urine owing to the increased excretion of acids by the skin in perspiration; the fall of acidity, or more accurately the increased alkalinity of the blood, allows the passage of an excess of uric acid through it, and this is accompanied by a fall of urea and the presence of more or less marked feelings of fatigue.

Here then, is the physiology of fatigue, depressed and deficient circulation in the muscle and nerve tissues owing to excess of uric acid in the blood; and this is obviously the explanation of the great

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[1] *Journal of Physiology*, vol. viii., p. 215.
[2] *Ibid.*, vol. xv., p. 167.

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disinclination for bodily and mental exertion which accompanies the uric acid headache, or mental depression due to the same cause.

But if fatigue is thus due to the presence of excess of uric acid in the blood, and if opium and cocaine can for a time abolish fatigue by keeping the blood clear of uric acid, it follows that fatigue will be absent, or very slight, so long as uric acid is absent from the blood, no matter what method is adopted for bringing about this result.

And as there are plenty of ways of keeping the blood clear of uric acid, it follows that there are also plenty of ways of preventing fatigue besides the use of opium or cocaine, or any drugs which act in the same way.

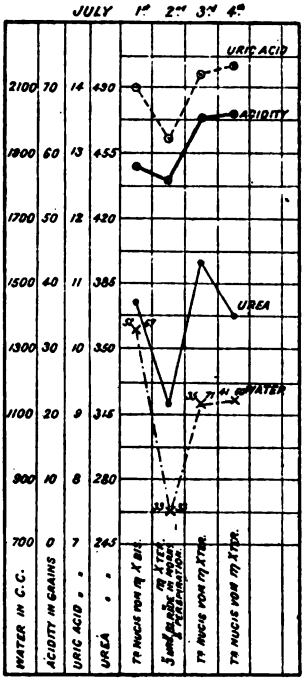

FIG. 39.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA (MORNING).

Opium and cocaine keep the blood clear of uric acid by raising the acidity, they thus counteract the effects of exercise and prevent the blood becoming a good solvent of uric acid as its result.

But there is obviously another way of keeping the blood clear of uric acid under these conditions, namely, by previously clearing out

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by means of solvents all the uric acid available to be got into solution by the rising alkalinity of the blood which the exercise produces.

Now, the most powerful solvent and excretant of uric acid is salicylic acid or one of its salts, and if these are given for four to five days before the exercise is taken, so as to sweep out all the uric acid available for solution in the blood, and if the drug is left off on the day that the exercise is taken, some very remarkable results are obtained.

First of all there is a great fall in the excretion of uric acid, which always occurs after salicylates have been taken for a few days and left off, so that there is absolutely no uric acid to come through the blood as the result of the rising alkalinity of exercise and perspiration (see fig. 8).

And with this condition of things there is almost complete absence of fatigue, even with the most severe exercise and the most profuse perspiration, and muscle power and endurance appear to be increased at least 50 per cent.; and further, there is this remarkable result, that whereas with the plus excretion of uric acid in ordinary exercise, there goes a great fall of urea followed by a rise next day; in the exercise undertaken in the absence of uric acid from the blood, and in which fatigue is more or less absent, there is either an immediate rise of urea or only a very slight fall.

It appears to me that in these facts we have an almost absolutely complete demonstration of the enormous influence exerted by uric acid on the metabolism, nutrition and function of the whole body, and we have also a complete explanation of a point in physiology which has been much disputed, viz., the influence of exercise on the excretion of urea.

I shall now give a few figures to illustrate the chief points I have mentioned.

In fig. 39 is shown the effect of three hours of bicycle work in the a.m. hours, and the result is a great fall in the excretion of urea, viz., 57 grs., followed by a rise next day of 78 grs. Take the fall from the rise and the result of the two days is an increased excretion of urea amounting to 21 grs.

Note further that uric acid is fairly high above urea, so that probably 4 grs. of it passed through the blood on the day of exercise.

In fig. 40 is shown in contrast with the above, the effects of three hours' bicycle exercise in the p.m. hours of the day; the amount of work done in the two cases is as nearly as possible identical.

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Here we see a fall of only 36 grs. followed by a rise of 60 grs. next day, and subtracting the former from the latter we get a rise of 24 grs. of urea as the result of the two days, so that while the amount of exertion was as near as possible the same in both figures, the resulting increased excretion of urea was the same all but 3 grs. The point which these figures are intended to illustrate is that for the same amount of exercise the fall of urea that results is greater when the exercise falls in the a.m. hours than when it falls in the p.m. hours, and that this is due to the fact that there is generally more uric acid in the urine and blood in the a.m. hours than in the p.m. hours (see figs. 1, 2, and 3); for we shall presently see that the fall of urea that accompanies

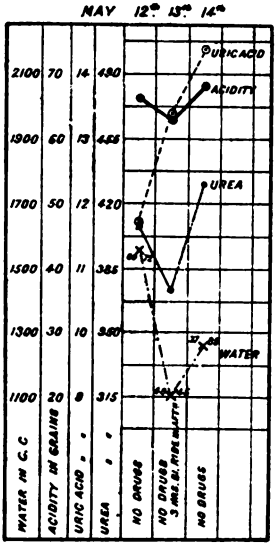

FIG. 40.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA (AFTERNOON).

exercise and fatigue is entirely dependent on the amount of uric acid in the blood, and that the amount of fatigue produced by any given exercise varies absolutely with the fall of urea, and is also therefore dependent on the amount of uric acid in the blood.

And this is no chance result of a single experiment, for I have been working at these points for several years, and it was the remarkable fall of urea that always accompanies exercise in the a.m. hours that first drew my attention to the subject.

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I will merely remark in this connection that Dr. Vaughan Harley has pointed out,[1] that less muscular work can be done at 9 a.m. than at 11 a.m., and that muscle power rises from 9 to 11 a.m., and that there is also a notable fall in muscle power at 4 p.m. And it is a remarkable fact that there is generally more uric acid passing through the blood at 9 a.m. than at 11 a.m., and about 4 p.m. there is generally also a temporary rise in the excretion of uric acid (afternoon alkaline tide, see fig. 1).

Again, I think that almost everyone must have made this clinical observation that children are often dull and heavy, and disinclined for both mental and bodily exertion in the a.m. hours when much uric acid is passing through the blood; while the same children are lively and bright and can hardly be restrained in the p.m. hours when there is but little uric acid in the blood.

A priori one would expect that the facts would be exactly the reverse, for in the a.m. hours the child has just been refreshed by a long night's rest, and in the p.m. hours it has borne the burden and heat of the day.

We see then, that in physiological conditions exercise undertaken in the a.m. hours generally causes great fatigue and a more marked and decided fall in the excretion of urea than similar exercise undertaken in the p.m. hours.

We shall now see that if measures are taken to keep the blood clear of uric acid during the exercise it will be accompanied by little or no fatigue, and will also produce little or no fall in the excretion of urea.

I have already referred to the action of opium, and the fact that it clears the blood of uric acid by diminishing the alkalinity of the blood.

Now, the action of opium in preventing fatigue is so well known that I wished to give a figure showing its effects on the excretion of urea and uric acid under exercise in myself, but I was met by this difficulty.

My diet is one in which milk is almost the only animal food, and I further consume a considerable quantity of fruit, and the result is that I have a large introduction of alkaline bases and but a small introduction of acids and acid salts such as the phosphates and sulphates of animal tissues; the consequence is that the acidity of my urine is much lower than that of those who eat ordinary diet, and the alkalinity of my blood probably much greater.

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[1] *Lancet*, 1884, vol. i., p. 1199.

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Hence I found that opium (in such doses as I cared to take), had comparatively little effect on the acidity of my urine, and as it thus affected the alkalinity of the blood but slightly, it failed to clear the blood of uric acid, and also failed to prevent fatigue and a fall of urea, when exercise was taken.

It may be objected that the rise of acidity in fig. 15 is well marked, but this was obtained some years ago when my diet contained more animal food than it does at present.

I therefore turned aside and selected a drug which acted independently of acidity and cleared the blood of uric acid; viz., mercury, though other metals as copper, zinc, silver, would have done equally well, and I have no doubt that the action of these metals in forming insoluble compounds with uric acid, accounts for the so-called tonic effects of small doses of these metals or their salts.

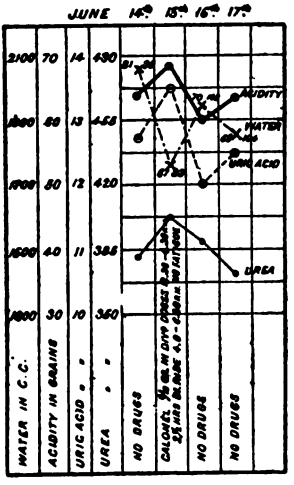

FIG. 41.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA AFTER CALOMEL.

I have pointed out that the urates of mercury are insoluble, and fig. 41 shows its effect in the form of calomel on the excretion of urea under exercise, and we see that there is an immediate rise of urea to the extent of 23 grs. followed by a fall next day; and with this rise of urea there was not only absence of fatigue but a feeling of increased muscle power and endurance.

But there are other ways of keeping the blood clear of uric acid

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besides giving mercury, opium, or other drugs which directly or indirectly diminish the solvent powers of the blood for uric acid.

And perhaps the best way to accomplish this is to take a course of salicylate of soda for four or five days before the day on which the exercise is to be taken, and then on the day of exercise stop the drug; the result is that uric acid falls very low, generally considerably below urea, and there is little or none to pass through the blood, and under these conditions fatigue is for many hours completely absent even in spite of severe exertion with perspiration, and the day's excretion of urine shows that there is also little or no fall of urea, or even a rise.

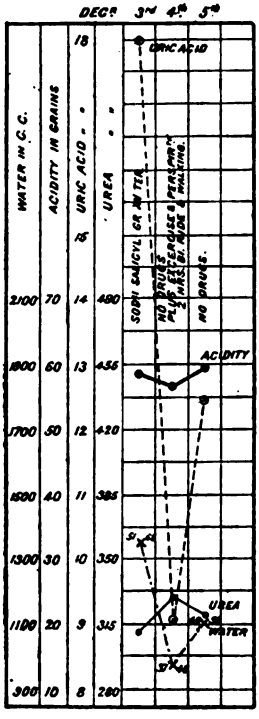

FIG. 42.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA AFTER A COURSE OF SALICYLATES.

Fig. 42 shows the effect of some exercise taken the day after a dose of salicylate, which had caused a very large excretion of uric acid; on the day of exercise the uric acid fell greatly and was

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slightly below urea, and with this there was an immediate rise of urea to the extent of about 19 grs. followed by a fall next day.

I have made similar experiments on numerous occasions, but shall only shortly mention my results in one more.

On the 10th of June, no drugs having been taken for several days, I rode 35 miles on a bicycle, the exercise beginning about 11 a.m. and ending about 5 p.m., with a considerable rest in the early part of the afternoon. This produced a fall of urea = to 27 grs., followed by a rise of 52 grs. next day, and the same rise was maintained on the following day, though this was partly accounted for by further exercise.

On the 24th of June, after a four days' course of salicylate of soda and the drug having been left off, I rode at about the same hours of the day 45 miles on a bicycle.

The daily curves show uric acid decidedly below urea and a fall of urea equal to 18 grs. followed by a rise of 23 grs. next day, and 70 grs. the day after.

My notes show, however, that on the day this exercise was taken, my food was unfortunately deficient for at least one meal, owing to my having accidentally left behind part of my supply, and but for this I think that there might have been no fall of urea on the day of exercise, and a greater rise on the day that followed it. As it is, however, the difference between a fall of 27 grs. for 35 miles and a fall of 18 grs. for 45 miles, is sufficiently marked, and on the 45 mile day there was little or no fatigue in spite of severe exercise and perspiration, till supplies of food began to run short.

I have also been told by Dr. W. Kidd, of Blackheath, that he has had somewhat similar experience with salicylates in that having taken these drugs for several days for uric acid headaches from which he suffered, he was surprised to find that he was able, though quite out of training, to ride 45 miles on a bicycle with as much or more ease than he had previously been able to ride 20 miles.

There is one further way in which the amount of uric acid in the blood, or available for solution in it, can be diminished, and that is by diminishing the daily introduction of uric acid (see *Journal of Physiology*, vol. xv., and *Brit. Med. Jour.*, December, 1894), and this is an experiment which is constantly being performed for us by others; I refer to vegetarianism. And in the second edn., p. 163, I have referred to the fact that in a long distance walk which excited some interest, and which is mentioned in the *Lancet* (1893, vol. i., p. 1396), the winners out of a large number of competitors were vegetarians.

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And in this country also, though vegetarians are quite insignificant as to numbers, they are not very rarely, I think, seen in the front of competitions in endurance.

It is precisely in the long distance that the absence or relative absence of uric acid from the blood tells; the meat eater will do very well for half an hour or even an hour, the relatively low alkalinity of his blood suffices to keep it pretty free from uric acid for that time in spite of the exercise, but once his alkalinity rises decidedly the inevitable collæmia results, and he is then quickly outpaced by his vegetarian competitor. Of course training counts for something, and one of the effects of training, *i.e.*, of regulated daily exercise, is to provide for a free excretion of uric acid more or less every day; so that the man who is in training will not have so much uric acid in his body available for solution in his blood as the man who, being on the same diet, starts for his race without any training, direct from sedentary work.

But those who have been accustomed to the stimulation of animal flesh and have mistaken this stimulation for strength, have evidently the greatest difficulty in believing that anyone can possibly be strong and fit for exertion on any other diet; thus a patient of mine, whose life was sedentary, had a beef-eating friend staying with him who prided himself on his walking, and, to escape further chaff on diet matters, my patient accepted his challenge to have a good walk; the result was that my patient walked him off his feet with comparative ease, and when some 20 miles had been covered the beef-eater acknowledged that he was tired and did not care to go any further.

And Professor Windle, of Birmingham, told me last autumn, when he had been on diet about twelve months, that 75 miles on a bicycle, half of it against a strong head wind, did not now suffice to produce fatigue, and that in fact, in his experience just as in my own, the old severe fatigue compelling an immediate rest at all costs was now unknown.

In my own experience, also, exposure to heat during exercise has now comparatively little effect, instead of producing utter exhaustion and a speedy breakdown, it rather improves the pace and does not interfere with endurance; in old days it quickly produced such extensive and severe collæmia that further effort became impossible, but now there is no material for such collæmia, and any little uric acid still left has its solubility improved by the heat, so that collæmia is prevented by this instead of being produced.

And under these conditions exercise is now always accompanied by an immediate rise in the excretion of urea, showing that waste

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products are at once removed from the muscles, and they are thus able to continue the production of force almost indefinitely.

Further instances of the same thing have been brought into great prominence in the daily papers by the recent war between Turkey and Greece; one could scarcely open a paper without seeing reports from the doctors of the wonderful vitality of the Turks, of their powers of endurance without food, of their fighting and marching after the receipt of serious wounds, and last, but not least, of the way in which they recover and their wounds heal, so that with them it is not a matter of shall I recover or shall I die, but shall I be well in time for the next battle.

I have absolutely no doubt that this magnificent nutrition and power of endurance, this resistance to depression and shock after injury is due, all entirely due, to the complete absence of collæmia which a uric acid free diet can alone produce.

Here the free capillary circulation so essential for the repair of wounds, which English surgeons have to produce with opium, is possessed by these Turks, not only for a few hours while under the influence of a drug, but every day and all day from birth to old age; and for similar records in the medical papers see, among others, the *British Medical Journal*, 1897, vol. i., p. 1219.

And yet similar demonstrations of magnificent vitality and powers of endurance have been given over and over again in the history of the world, and have fallen absolutely without result on the blind eyes and deaf ears of those deluded by flesh and alcohol.

I have even found some to argue that as there are too many people in the world a diet which shortens life, even if it also makes it miserable, is not altogether a disadvantage; these people, however, overlook the fact that certain portions of the world would support many times the number of people now existing on them if they were frugivora in place of carnivora; hence the excess of population is relative to the diet, and not absolute.

But indeed it would be laughable to hear some of these beef-eaters talk, if it was not also sad; many of them, I verily believe, think that they can control the world and arrange everything better than omniscience, they almost condition the revolution of the earth in its orbit, and the motions of the satellites of Jupiter; in a word they differ but little from the common asylum specimen, who fancies himself the creator and upholder of the universe; and yet with all this it is often only too painfully evident to their physician that they are practically powerless to control even their own appetites.

It is all of a piece with the insane self-glorification which still

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makes even an educated man ask you what his fellow-creatures have been sent for, if he may not eat them. What an idea such a man must have of the attributes of omniscience and omnipotence to credit them even for a moment with such doll's-house philanthropy.

But even this does not include all the advantages to be reaped from a uric acid free diet, for not only is there no fatigue during the exercise to-day, but there is also no stiffness and rheumatism after it to-night and to-morrow, which gives once again a striking demonstration of the intimate relationship between rheumatism and uric acid. On ordinary diet I never got hot in summer with subsequent exposure to cold or a draught without a stiff neck, some lumbago, or other trouble. Now all such troubles remain absent even after the the most severe exertion and perspiration with subsequent exposure to cold; and Professor Windle is equally emphatic on these points, and he now never suffers from stiffness or rheumatism even from exposure to cold and wet during and after exercise.

And now I may as well answer a question which is certain to be asked by someone, viz.: How is it that horses suffer from rheumatism, not only arthritis, but endo-carditis, peri-carditis and all, and yet they are vegetarians and ought undoubtedly, so it may be said, to be free from these troubles?

Now, the answer to this is not really difficult after a careful study of fig. 65, where it appears that I got a very severe attack of gout, not from the introduction of uric acid, as my diet was practically free from it, but from taking an excess of albumens, and consequently forming too much uric acid, some of which I failed to excrete.

Now, horses live in an artificial state of things, and some of their foods are highly nitrogenous (beans and cereals), and these are given in a rule of thumb manner without any real reference to the nitrogen required for body weight, or the work that has to be done, and there can be very little doubt that if allowed to satiate themselves on such strong foods they often get too much albumen just as I did, and will consequently both form and retain too much uric acid.

And not only so: but when fed on dry foods and deprived of fresh vegetable substances such as they would get in a state of nature, they may also suffer from a relative deficiency of alkaline salts in the blood, and thus have also increased retention of uric acid.

Then it is clear from the record given a little further on that horses suffer from fatigue and the sleeplessness it produces just as men do, and that as in men also these symptoms can be relieved by opium.

In a word, they have uricacidæmia and its results, and when

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exposed to cold and wet after fatigue they also get, just as man does, a precipitation of this urate upon their joints and other fibrous tissues.

And the manner in which horses are exposed to wet and cold after fatigue is known to all; if any part is covered it is the back and hips, important no doubt; but the fibrous tissues of the limb joints are left absolutely exposed.

Only in the case of the horses of the rich is the precaution of keeping up some gentle exercise taken, and it is just the overfed horses of the rich that specially need such care, while the less overfed cab horses may have relative immunity both from fatigue and rheumatism.

As we shall also see in chapter xvii. some of the vegetarian natives of India suffer from gout, rheumatism and stone for exactly the same reason that horses suffer, and in the case of the natives statistics show that those suffer most from these things who live on the food which is the richest in nitrogen.

Of course, it goes without saying that with too low urea nothing can be done; *nihil a nihilo fit :* but then my point is that my urea is not low, it remains at or about the physiological level of 3·5 grs. per lb. per day; but I get the nitrogen necessary for this from sources which introduce into my body as little as possible of unnecessary uric acid; that is to say, I avoid meat, meat extracts, soup, beef tea, and strong tea or coffee.

But to return: these facts seem to demonstrate pretty clearly that fatigue is proportional to the amount of uric acid available for solution in the blood at the time that any given muscular exertion is undertaken; and that the immediate effect of the exercise on the excretion of urea is similarly directly determined by the amount of uric acid present.

I would point out that these results of mine correspond absolutely with those of Parkes, for he often found a diminution of urea during the exercise, followed subsequently by a slight rise; and they serve to explain also most completely the conflicting evidence and contradictory results of other observers.

Such contradictory results can now be absolutely explained, for we see that they are simple effects of the fluctuation in the excretion of uric acid, and if you control the uric acid you can control the effect of the muscular exercise upon the urea; and not only that, but also the fatigue which the exercise produces.

My results bear also in a most important manner on the explanation that is to be given of the results obtained by Fick and

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Wislicenus in their celebrated experiment, in which they performed a certain amount of work on a non-nitrogenous diet and estimated the nitrogen excreted, with the result that the excreted nitrogen fell very far short of the amount required to account for the work performed.

From this experiment it has been concluded that their muscular energy had other sources besides their proteid metabolism, and this may still be the correct conclusion, though the results I am now bringing forward must, I think, be regarded as modifying it very considerably.

In the first place, my experiments show that exercise always produces sooner or later an increase in the excretion of urea, and I have absolutely no doubt about this fact, as I have been watching it for years in my daily work at the excretion of uric acid and urea, and have hundreds of curves to prove it; I am also at this point in complete accord with the results obtained by North[1] in his elaborate and careful experiments; as he showed that in times of rest there was a storage of nitrogen in the body and that after exercise there was an increased excretion of a roughly corresponding amount.

The results I now bring forward further show that the time at which this increase of urea is excreted depends absolutely on the amount of uric acid present in the blood. Clear the blood of uric acid by no matter what means, the exercise will be accompanied by an immediate rise of urea; bring a lot of uric acid into the blood, and it is easy to do this (see figs. 24 and 25); there will be an immediate fall of urea, followed by a rise next day.

Clearly then, the differences and contradictions between the results of previous experimenters were due to ignorance of this fact, and this explanation has a special and important bearing on the experiments of Fick and Wislicenus, for they did their work on a non-nitrogenous diet.

Now, it follows simply from my previous researches that one effect of placing themselves on a non-nitrogenous diet would be a great fall in the acidity of the urine, and a corresponding increase in the alkalinity of the blood; and the natural and only possible result of this would be (as they had exercised no care to clear out uric acid beforehand) that their blood would be forthwith flooded with a more or less large amount of uric acid from the stores in their bodies; and the result of this would be, as we have seen above, that muscular exercise would be accompanied by a great and immediate fall in the excretion of urea.

[1] "Proceedings of the Royal Society," 1885, p. 501.

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No doubt next day, as in my experiments, there would be a rise that more than compensated for the fall; but these experimenters estimated the nitrogen of twelve hours before labour, of three hours during labour, and of six hours' rest after labour, and drew their conclusions from these; but this period would not be nearly long enough to include the rise that followed the fall, hence the nitrogen they obtained was very far short of the amount really excreted as the result of the exercise taken, and their results are to this extent fallacious.

Though this argument applies to their experiments as a whole, it is interesting to note that they did get an immediate increase of the excreted nitrogen at the time of the exercise, thus :—

[1] Nitrogen excreted in grms. per hour.	Fick.	Wislicenus.
In 12 hrs. before the labour	·575 gr. per hr.	·556 gr. per hr.
In 3 ,, labour	1·103 ,, ,, ,,	1·043 ,, ,, ,,
In 6 ,, rest after labour	·405 ,, ,, ,,	·403 ,, ,, ,,

But this no doubt corresponded absolutely with the excretion of uric acid and the amount passing through the blood; for though they took no nitrogen during the experiment, the nitrogen they had previously taken served (as shown by North) to keep them going, and prevent any great increase of the alkalinity of the blood till the exercise had been continued for some time; but towards the end of the exercise, and still more in the rest after it, there would be a great rise in the alkalinity of the blood, increased by the absence of nitrogenous food; and it would be flooded with a correspondingly large amount of uric acid.

The result of this would be just what the above figures show us, a great fall in the excretion of nitrogen in the hours that follow the labour; for during the hours of labour it was upwards of 1 gramme per hour for each of the experimenters, but in the rest which followed, it fell to less than half a gramme per hour.

If the hours of labour had been examined hour by hour I have no doubt that the larger excretion of nitrogen would have been found in the first hour and a-half or two hours, and that after that there would be a considerable fall; and if uric acid and urea had been separately estimated uric acid would have been found below urea (in the relation 1—35) at the beginning of the labour, but far above it towards the end and in the rest which followed (see also previous remarks about vegetarians and meat-eaters).

As I have already pointed out, the amount of uric acid in the

[1] From figures given in Prof. Foster's "Textbook of Physiology," 1877, p. 325.

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blood not only controls the excretion of urea under exercise but under all conditions from hour to hour and day to day, and practically every rise of uric acid is accompanied by a fall of urea, and every fall of uric acid by a rise of urea.

In attempting to verify these statements, however, those who come to the subject *de novo* must bear in mind certain simple propositions, viz., that the rise or fall of uric acid must be sufficiently decided to overcome other concomitant fluctuations in a reverse direction; for instance, it would require uric acid to be very high indeed to overcome the rise of urea that generally follows the day after exercise; but in pathology uric acid may be high enough even to do this if its rise is in part the result of a complete upset of gastro-intestinal digestion. On the other hand, if uric acid has been for some hours above urea, and is brought down below it suddenly with any drug, the probability is that there will be a fairly marked rise of urea corresponding to its fall; but if uric acid has been close to urea for some hours before the drug is given to bring it lower, the rise of urea may be too small to show in the curves.

And it was, as I have pointed out, the rise of urea that followed the ingestion of uric acid that was thought by Sir A. Garrod and other observers to show that the uric acid given had been converted into urea; but we now know that any acid or metal which clears the blood of uric acid will produce a similar rise of urea, and yet these substances introduce no fresh nitrogen into the body, and are incapable of conversion into urea.

We also know that uric acid taken by the mouth acts as an acid and for a time also clears the blood of uric acid, and so causes a rise in the excretion of urea; but the uric acid taken will pass out in the urine a few days later, and will increase the ordinary excretion in proportion to the amount that was swallowed (see figs. 23 to 29; also *Journal of Physiology*, vol. xv., p. 167 and 170; and *British Medical Journal*, December, 1894).

If then, uric acid in the blood controls, as above pointed out, from hour to hour, day to day, and during and after exercise the excretion of urea, we may consider for a moment the way in which it produces such effects.

Now I have for years been pointing out that uric acid in the blood controls the circulation throughout the whole body, and that its excess in the blood is at all times accompanied by high blood pressure and deficient capillary circulation, the latter being the cause of the former.

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And have further said that the best proof of this is to be seen in the fact, which anyone can verify in a few hours of work, that the hourly and daily excretion of water by the kidney varies inversely with the uric acid also excreted from the kidney.

And I believe that there can be no explanation of this fact save that I have given, that the uric acid directly or indirectly obstructs the flow of blood through the capillaries of the kidney and thus prevents the passage of water out of the blood into the urine.

Here, again, investigators must bear in mind certain cautions; first, that when there is no excess of water in the blood, freeing the capillaries by clearing the blood of uric acid will not produce a diuresis; and second, that when the blood is cleared of uric acid even for a short time, there may be so great a diuresis that if care is not taken to separate excretions accurately, the urine of several hours may seem to be profuse, though the uric acid during the major part of this time is not at all scanty: but separate accurately from hour to hour, or if necessary from half hour to half hour, and you will see that the great diuresis did correspond to low uric acid, and there are plenty of figures which show this (see fig. 3 and my remarks about it).

But apart from such sources of fallacy the uric acid and urinary water do vary inversely in everyone from day to day, or hour to hour, and every drug that clears the blood of uric acid produces a diuresis if there is any water to be run off; and the action of nearly all the best known diuretics is a simple illustration of this law.

We have also in fig. 5 independent evidence that exercise increases the amount of uric acid in the blood, for it increases the distance between the temperatures in the mouth and rectum; it also appears to do this to a greater extent in the alkaline tide hours than in the evening hours, the exact parallel of its effects on urea excretion and fatigue.

If then, it be granted that uric acid in excess in the blood does obstruct the circulation in the capillaries of the whole body, it is easy to see how it produces fatigue and the fall of urea which accompanies muscular exercise, except when the blood is specially cleared of it.

For obviously deficient circulation must mean deficient metabolism in all the organs and tissues of the body, and deficient removal of waste products from these same tissues, and it is in this way that excess of uric acid in the blood diminishes the excretion of urea during exercise and produces fatigue. It no doubt affects both the

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muscular and nervous tissues at the same time, producing both fatigue of body and dulness and depression of mind.

The effect then of uric acid on tissue metabolism in the human body is the same as if one put a wet blanket on the kitchen fire and shut all the flues to cut off the air supplies; the result is slow and deficient combustion. The wet blanket corresponds to the products of previous metabolism which are left to clog the tissues so long as the circulation is defective; and the removal of the wet blanket is the cause of the rise in urea which accompanies the next fall in uric acid; and obviously this rise of urea is proportional not necessarily to the fall of uric acid but to the amount of interference with metabolism that has previously taken place in the tissues. Hence the rise of urea that follows the clearing up of collæmia is generally only a matter of 10—15 or 20 grs. in physiological conditions; but in Bright's disease where the failure in metabolism and removal of waste products has been of longer duration and of much greater extent, the rise may amount, as we shall see in chapter xiii., to 100 grs. or more.

I conclude, therefore, that the effect of exercise is to increase the formation of urea, and that if there is a free circulation through the tissues owing to comparative absence of uric acid from the blood, this urea will pass almost at once into the urine and be excreted. With this condition of things will go comparatively little fatigue, and greater and longer continuance of exertion will be possible; but if there is a lot of uric acid in the body or food, so that the rise of the blood's alkalinity, which the exercise and perspiration produce, can dissolve a large quantity and bring it into circulation, then you will get deficient circulation in all the tissues, and with this a fall in the excretion of urea and great fatigue, because the tissues are clogged with waste products; so that continued exertion may be almost impossible, and if persevered with may lead to syncope and more serious troubles.

Further, as we have seen above, it is possible by controlling the uric acid to control the result.

Professor M. Foster, writing on the physiology of weariness in 1893,[1] attributes it to the presence of a poison in the blood. I believe my researches now suffice to demonstrate that the poison is uric acid. I may point out that these facts explain completely the observed relations between fatigue and weather changes., *i.e.*, that fatigue is greater in warm and less in cold weather, for obviously

[1] *Lancet*, 1893, vol. i., p. 1457.

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the warmer the weather the greater will be the perspiration that any given exertion produces, and the greater the perspiration, the greater will be the rise in the alkalinity of the blood, and the sooner, other things equal, will it contain excess of uric acid.

On the other hand, a cold wind or a cold frosty day will tend to diminish perspiration, and hence will reduce and delay the increase in the alkalinity of the blood; under these conditions much more exercise can be taken without fatigue just as with mercury, opium, &c., and for the same reasons; for the muscles are kept longer free from the deficient circulation, nutrition and metabolism, which collæmia produces.

The argument that has been here applied to the production of energy by muscles, holds also probably for the production of heat by these and other tissues. That is to say, when the blood is clear of uric acid, there will be increased production both of energy and heat throughout the tissues of the body; therefore external cold will increase the production of heat and external warmth will diminish the production of heat just as we have seen that they also increase and diminish the production of muscular energy, and in the action of uric acid on the vessels we have at once established a regulating mechanism that damps down the fires of life when they are not wanted, but allows them to burn brightly when an increased production of heat is required.

I will now shortly mention a case of slight fatigue (that of Weston, the pedestrian), the signs of which have been carefully recorded by the late Dr. Mahomed (*British Medical Journal*, March, 1876), with the object of showing that these signs and symptoms are practically those of collæmia. Thus it is recorded of March 10 and 11 that he lost weight, that he became sleepy, that his pulse tension "was now very considerably increased," that there was a coincident fall of temperature. "His hands felt cold instead of glowing as heretofore; he complained of feeling chilly and required more bed-clothes. The second sound of his heart was accentuated, and the first a little prolonged." Anyone can now recognise these as the signs of collæmia, and I have no doubt that they were accompanied by a fall in the excretion of urea, and were contemporaneous with and due to an excess of uric acid in the blood. They are the common symptoms of the uric acid headache, and the causation of most of them has already been fully gone into.

On March 12 the pulse tension had again become low; with this his temperature went up, and his extremities became warm. "After this he awoke much refreshed, and continued to walk well and easily

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to the end of the match. This probably was coincident with the change in arterial tension."

I quite agree as to these changes of condition being coincident with the change in arterial tension, but they were much more than that, they were absolutely due to it; once uric acid was cleared out of the blood the capillaries were freed, the nutrition of the muscles and nerve centres improved, and the signs of fatigue vanished.

One of Weston's competitors suffered more severely from the same symptoms, having probably a more severe and prolonged collæmia, and had to give up the match.

Among other symptoms of this condition specially mentioned are a feeling of weight and discomfort in the præcordia, cough with increased secretion of bronchial mucus (see chapter ix.) and albuminuria. The pulse then requires much pressure to develop it "on account of the fulness of the artery," in other words, high tension.

Cases in which fatigue is fatal, as in that about which a paper was read by Dr. Dukes at the Royal Medical and Chirurgical Society, May 9, 1893 (see *Lancet*, 1893, vol. i., p. 1136), present, I believe, but a mere exaggeration of the above named symptoms, and even the disintegration of the blood mentioned by the last named observer may be but a further stage of the blood changes which may produce the albuminuria noticed by Mahomed, or the blood changes in anæmia, of which I shall have to speak presently, or the still more marked changes in the blood seen in paroxysmal hæmoglobinuria, which I believe to be paroxysmal collæmia (see chapter xii.).

The same explanation will obviously apply to a case recorded by Dr. Lee Dickinson (*Lancet*, 1894, vol. i., p. 1250), where transient hæmoglobinuria followed muscular exertion taken while out of training.

But if fatigue is due to collæmia and the obstructed capillaries and deficient circulation in important structures which it brings about, it, just as is the case with mental depression, should be proportional to the amount of uric acid in the blood. And the amount of uric acid in the blood is proportional to two things: (1) the amount of uric acid in the body available for solution in the blood, and (2) the importance of the fall in acidity which increases the solvent powers of the blood.

Now, other things being equal the fall in acidity will be greater the greater the perspiration, and perspiration will be greater in hot weather than in cold, and greater also for the same exertion in a man who is not in training as compared with a man who is. Hence fatigue is greater in warm moist weather as noticed by Dr. Dukes,

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and those not in training, as in the above mentioned case, will have more collæmia and break down sooner than those who are.

But we have seen in chapters iii. and iv., that the uric acid in the blood is to a certain extent proportional to the amount swallowed in the food, and that those swallow most who live on butcher's meat and other animal foods, while those who are vegetarians swallow probably much less (see also chapter xvii.). This may, I think, in part account for the reported victory of the vegetarians in a long distance walk previously referred to (see *Lancet*, 1893, vol. i., p. 1396).

The fact that fatigue means an excess of uric acid in the blood (collæmia) suffices to explain at once its relation to acute rheumatism. Let there be exercise and perspiration with increased alkalinity of the blood and uricacidæmia, and let there supervene on this anything such as cold or fever which causes a sharp rise in the acidity of the urine and an equally marked fall in the alkalinity of the blood, and we have all the factors in the natural causation of acute rheumatism.[1] The sharp fall in alkalinity will drive all the uric acid out of the blood into the joints, and the effect on the joints will be proportional to the amount of uric acid in the blood and the rapidity with which it is driven out, and, as I have said, nature's methods in this matter can be imitated to any required extent.

As already said, if you take care to remove the available uric acid before beginning the exercise, almost an unlimited amount of exercise with perspiration may be undertaken without fatigue, and a course of salicylates will, as we have seen (fig. 42), not only do this, but it will prevent the exercise from being followed by any stiffness or myalgic pain, so that these are the physiological counterparts of rheumatism. And if all such troubles are proportional to the amount of uric acid in the blood, it is little wonder that a somewhat vegetarian diet has been found to do much good in pregnancy and to moderate greatly the pains and troubles of parturition (*British Medical Journal*, 1895, vol. ii., p. 99), where the result of such diet is said to be "a remarkable feeling of well-being; the sense of fulness, bearing down, and weariness, thirst and constipation soon disappeared, and the patients have been able to walk many miles up to the eve of confinement."

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[1] See also Dr. A. S. Eccles, *British Medical Journal*, 1891, vol. i., p. 1075; also "The Practice of Massage," by A. Symons Eccles, Macmillan, London, 1895, pp. 85 and 198, where many interesting facts about fatigue and rheumatism and their relations to other conditions are mentioned.

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And if I am correct, they would not only escape the above troubles but during and after confinement would also escape the headache, post-partum hæmorrhage, depression, convulsions, mania or albuminuria, in a word, collæmia and its results which on ordinary diet are far from uncommon; and indeed, I have myself steered more than one woman, the subject of Bright's disease, safely through pregnancy and parturition by means of a milk diet.

Thus the effects of uric acid enable us to account for every symptom and pathological relationship of fatigue. But fatigue pushed to extremes produces syncope, and this syncope may continue and end in death as in the case recorded by Dr. Dukes.

And the causation of this syncope is, as we have seen, that, from causes which differ from physiological conditions merely in degree, the blood is flooded with uric acid. This obstructs all the capillaries, hinders the circulation through the muscles and nerve centres and the lungs, and other organs, and also produces high blood pressure and alteration of heart sounds as in the case recorded by the late Dr. Mahomed.

If the collæmia gets more severe the heart falters and flutters, as I have noticed that it does under these circumstances in myself (see fig. 36), and finally, if there is no relief it stops, and syncope supervenes. Speaking of dilatation of the heart, Sir W. H. Broadbent says: "It is usually gradual in its development, but acute dilatation of the heart is a more common occurrence than is generally supposed, *and when it is induced by effort antecedent high arterial tension is, according to my experience, a constant predisposing factor.*" ("The Pulse," p. 168.)

But if the syncope of fatigue has this causation it seems very probable that syncope met with under other conditions may have a similar causation.

I have already (chapter vii.) mentioned the pulse of epilepsy and other convulsions, its slowness and high tension, and the late Dr. Moxon's suggestion that stoppage of the heart is the cause of the fits, and I would further point out that my own experience seems to show that the heart specially flutters and gives signs of discomfort as the tension rises, that is to say, as there is a change from low to higher tension. I have also mentioned the syncope of bathing. There is another condition in which syncope is not uncommon, namely, convalescence from acute disease, and here also it is associated with high blood pressure and subnormal temperature, just as in fatigue. I make it a rule not to allow any convalescent to sit up or make any exertion till the temperature

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has risen to normal and remains there, for I believe, and indeed I know, that the heart is often affected, perhaps dilated by the high blood pressure, and that any effort may be the last straw.

And there is one other condition in which syncope sometimes occurs, namely, during or just after the administration of chloroform, which seems to me to have many points in common with the conditions named above, though as I have no personal experience worth mentioning, anything I say must be taken as suggestive merely.

What I would suggest is this, that chloroform frees the capillaries and lowers blood pressure (as appears to be well known), and I think that it may do this like so many other drugs mentioned in this volume by clearing the blood of uric acid.

Then when the chloroform is left off there will be a rise of blood pressure which I have spoken of in the case of other drugs as the rebound, and if this is great and rapid the heart will flutter and falter, and perhaps cease to beat.

Further, the fluctuation in blood pressure which the drug produces will be greater (other things equal) the more uric acid there is in the body and blood at the time it is administered, and the greater the fluctuation the greater the strain on the heart.

Taking this view of the matter, I was greatly interested by an article by Dr. R. Kirk, in the *Lancet*, 1893, vol. ii., p. 429.

In this paper he shows that in animals when inhalation of chloroform is discontinued the lungs are emptied of its vapour in 10-20 seconds, and a little after this the heart suddenly slows and becomes irregular, and there may be syncope. Further, the longer the inhalation is continued, the later does this slowing and irregular action of the heart appear, and he says, "the irregular action commences when the last drop of chloroform has left the blood."

This disposes once and for all of any idea that the irregular action is due to the chloroform, but if it is due to the rising pressure as I am suggesting, it is just what we should expect—indeed it almost amounts to a demonstration.

If the heart fails rapidly its action may become quick instead of slow, just as in other conditions where there is high blood pressure (see chapter v.).

And then with this failure of the heart the blood pressure will fall very greatly; but that there is rising blood pressure at the onset of the trouble is, I think, proved by the slowing of the pulse, in accordance with Marey's law (see chapter v.). While if the first event is a great fall of blood pressure, as Dr. Kirk seems to

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suppose, there is no reason why the heart should slow, and I have just pointed out that blood pressure is high and the pulse slow in the parallel conditions of fatigue, convalescence (post febrile bradycardia), and certain cases of epilepsy.

Now post chloroformal high tension differs from these chiefly in its rapid onset, and it is on this account likely, as my experience seems to show, to affect tho heart more severely.

Some extremely interesting cases bearing on these points were published by Mr. A. Wilson in the *Lancet* of November 17, 1894, and in a paper on "The Pathology of Chloroform Syncope" in the *Lancet* of February, 1895, I have referred to these and other cases in illustration of my argument.

In Mr. Wilson's Cases 1 and 2 we have, as he truly says, all the signs of primary failure of the circulation, and in his Case 6 we have this occurring as the patient is coming round and is sufficiently conscious to give a cry of pain; but whether in Cases 1 and 2 the syncope came on during slight breaks in the administration of the chloroform, as contended by Dr. Kirk, there is not sufficient evidence to show. With regard to Case 6 Mr. Wilson remarks that the syncope was due to the reflex inhibition of the heart by the pain, but that some blame must also be laid upon the semi-anæsthetic condition of the patient at the time, but I shall have to speak of these points again. It is interesting to note also that Mr. Wilson agrees with Dr. Kirk in looking upon a sudden quickening of the pulse as a danger signal.[1] Dr. Kirk also mentions in the reference just given the case of a patient who died from "the reaction which ensued when he began to breathe fresh air."

Then in the *Lancet* of November 24, 1894, there is the record of a case of syncope under chloroform in which nitrite of amyl averted a fatal result, and its effect is said to have been "almost instantaneous." I have elsewhere suggested that this drug acts by reducing the blood pressure and thus freeing the heart from its overpowering effects (for another case in which it was used with success see the *Lancet* of March 7, 1885). And even in the same number of the *Lancet* (November 24, 1894), there is the record of a case in which death ensued, and it is said with regard to the onset of the fatal signs that "the administration of the chloroform had been stopped," and in an annotation on the same case in the next number (p. 1291) further points of great interest are mentioned: (1) that she had taken chloroform with impunity on other occasions;

[1] The *Lancet*, June 23, 1894.

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(2) that she had been confined fifteen months previously and had recently lost a child, and was suffering from the depressing effects of grief; (3) that there was slight renal disease (and I note also that one of Mr. Wilson's cases suffered from chronic Bright's disease); and (4) that "before the dentist had touched the patient, although the chloroformist had taken away the chloroform from her face and pronounced her ready for operation, she suddenly became ashy pale, but respiration continued"; here, then, we have exactly the condition described and insisted upon by Dr. Kirk and Mr. Wilson.

Another death under chloroform—in which there was great difficulty in giving the anæsthetic owing to the nose being the point to be operated on, and where the patient, therefore, came round several times before the fatal event—is recorded in the *Lancet* of August 26, 1893, and similar deaths from too little chloroform or a lull in the administration, were discussed in 1892, and 1893.[1] I have mentioned above Mr. Wilson's opinion that in his Case 6 the syncope was due to the reflex inhibition of the heart by the pain; but it seems to me that a somewhat different relation between cause and effect to that he suggested, is possible. Thus I have said, with reference to the effect of high blood pressure on the action of the heart (fig. 36), that my own heart never falters or flutters except when there is high or rising blood pressure; but there is one condition I ought to have mentioned in which my heart does flutter or falter just as in pulse tracing A, fig. 36 (which shows well-marked high arterial tension), and that is during severe irritation of a sensory nerve. I happen to suffer many things with the dental branches of the fifth nerve, and I have several times noticed that with the most severe paroxysms of pain my heart falters and flutters just as it was doing when the above-mentioned pulse tracing was taken, for these cardiac irregularities, not being habitual with me, are always distinctly felt. Now, in the case of my own heart, was this a reflex, or was it due to rising blood pressure? If we may consider—and so far as I know, physiology does not negative the idea—that irritation of a sensory nerve causes a general contraction of arterioles and a rise of blood pressure, the cause was in both cases the same, and my heart fluttered under the dental pain for the same reason that it did so in pulse tracing A, because in both there was high and rising blood pressure. We can now fully appreciate the bearing of Mr. Wilson's Case 6. Here the patient was coming out of the chloroform anæsthesia, and blood pressure was

[1] *Brit. Med. Jour.*, 1892, vol. i., and 1893, vol. ii., p. 1452.

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therefore rising; suddenly to this was added severe irritation of the sensory nerves of the knee, causing an acute rise of blood pressure, and it was little wonder that the heart was thus completely overpowered and that syncope at once resulted, and death may no doubt occur when the heart is weak from the blood pressure effects of pain alone, as in a case recorded in the *Lancet*, 1896, vol. i., p. 1457, where death occurred a few minutes after the extraction of a tooth, no anæsthetic having been given. I quite agree with Mr. Wilson that one cause of death after chloroform is syncope, and endorse his valuable suggestion that syncope under other conditions should be studied to illustrate it; and if this is done many will, I believe, be astonished to find how large a number of syncope cases are preceded or accompanied by evidences of high and rising blood pressure (see previous quotation from Sir W. Broadbent, p. 288), and, if these can also be examined, by excess of uric acid in the urine and blood.

But those who are working at this matter will have no difficulty in getting records of similar cases, as the journals contain no end of them.

Thus in the *Lancet*, 1896, vol. ii., p. 881, there is the record of a fatal case under chloroform at the Royal Victoria Hospital, Netley, in which all the signs and conditions seem to have been observed most carefully.

This record states: "The breathing continued to be natural and regular for about one minute after the administration was commenced; the patient then made some slight attempt to cough and the breathing became irregular," and further on: "Immediately the breathing became affected the inhaler was removed," and again: "The moment the respiration became irregular the administration of the drug was stopped; a few seconds later the pupils dilated and the heart's action ceased, and the man was practically dead, although respiration continued for a few seconds longer."

Exactly so, but the error here was the removal of the inhaler and the stopping of the chloroform, and everything that followed, including death, was the result of this; a few seconds later there came the vapour reaction of Dr. Kirk, or what I call the rebound, with rapid rise of blood pressure, and before this the heart failed, and respiration continued, though it had been the first thing to become irregular, showing that in the first instance the respiration had not been really seriously affected.

It would be absolutely impossible to get a record reproducing more exactly every point brought out by Dr. Kirk's experiments on animals, and these experiments show us that such rebound is best

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prevented by at once resuming and steadily continuing the chloroform, except for the sudden withdrawal of which they would never have occurred.

And it seems probable from the considerations above mentioned that the rebound comes sooner the less of the chloroform has been given before it is withdrawn, and later the more long-continued the administration has been; hence it is probably more dangerous to suddenly withhold chloroform early in its administration, as in the above case, than later on, and this also will explain the observation of some anæsthetists that more patients die from too little chloroform than from too much, and the by no means unfrequent records in fatal cases that special care had been taken to give very little chloroform.

In the above case it seems probable that if the slight irregularity of the respiration and cough (probably indicating imperfect anæsthesia and a reflex from some mucus in the air passages) had been disregarded, and the chloroform quietly and carefully continued, the cough would have subsided and the anæsthetic could have been continued throughout the operation, and then in the rebound when chloroform was discontinued at the end of it, the rise of blood pressure would have come more gradually, and the heart would not have been overpowered.

Brigade-Surgeon Lieutenant-Colonel Stevenson who records the above case also mentions that he has seen another in which "the sequence of events was precisely similar; the pulse first stopped, then the respiration," showing how very frequent, relatively to fatal accidents with chloroform, such cases are; and all I have above suggested is a most simple deduction from the records of Dr. Kirk's experiments.

In a letter also which Dr. Kirk kindly sent me on the subject he mentions that further investigation seems to show that the blood pressure does not fall as the heart slows; in other words, it is just as I said, the heart slows because there is high blood pressure in accordance with Marey's law; but if the heart falters before the high blood pressure, if its systoles become imperfect and its action irregular, or still more if it stops altogether, then of course there is a fall of blood pressure.

The effect of high blood pressure on the heart is then either quick action or slowing; the former if it fails, the latter if it is able to withstand it, and obviously the higher the pressure the more likely is it to fail and quicken its action (tachycardia), and this is exactly what Dr. Kirk's results with animals show; with the highest

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blood pressure the heart's action is quick and irregular, with a slight fall of blood pressure it slows.

This also is exactly what we see in epilepsy in those cases where, as observed by the late Dr. Moxon, the heart stops; in these cases the heart has been seen to act slower and slower, and then it stops altogether (a mere exaggeration of the dropped beat in my own pulse, fig. 36), and down goes the patient insensible and convulsed from stasis and anæmia of the brain; then comes a great fall of blood pressure so that a wound ceases to bleed, this fall of blood pressure relieves the heart, and it begins acting again if the cerebral centres have not lost their functional activity; but if anything prevents it from starting again, death results. Similarly bleeding, as in a case of post-chloroformal syncope recorded in the *British Medical Journal*, 1896, vol. ii., p. 122, may relieve the heart by permanently reducing blood pressure, and in this case also the pulse stopped before the respiration.

Hence in such cases of post-chloroformal and other syncope from high blood pressure, holding the head down as the lowest point of the body gives the medullary centres some little blood, and possibly saves their functional activity till the heart has time to recover itself and life is continued.

Dr. Kirk also points out in his letter that in his experience, rabbits (herbivora) are not liable to the irregular action of the heart when the chloroform is withdrawn, while dogs and cats (carnivora) are very liable to it, which is again very strong proof of the causation I am suggesting.

For though the muscles of herbivora no doubt contain xanthin, as we get excess in our body from eating them, this is merely but a small residue remaining unexcreted at the time of death, and the quantity in their blood at any one time is always small.

In carnivora, on the other hand, there is a constant introduction of uric acid, while its excretion is, as I have shown (chapter ii.), liable to be affected by alterations in the alkalinity of the blood corresponding with similar alterations in the acidity of the urine; hence they are liable in a way that herbivora (at least in a state of nature) are not, to excrete less uric acid than they swallow, and to accumulate it in their bodies, and may thus have temporary excess in their blood at the time the chloroform is given.

Another condition in which syncope is known to occur, and which it is interesting to bear in mind while considering these effects of blood pressure, is that which comes on in church while kneeling with the arms raised, and Marey also points out that this

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position impedes the circulation in the raised limbs, raises the blood pressure and slows the heart, and here again the slowing of the heart may be preparatory to its becoming quick or irregular, or stopping altogether.

Further evidence pointing in the same direction is, I think, to be seen in the fact that nitrite of amyl is useful in this chloroform syncope, and there is probably no drug which would more quickly relax the arterioles, free the capillaries, and prevent the rise of blood pressure; while it is hard to see how it can do good if the blood pressure is already low.

Speaking of nitrite of amyl reminds me of an experiment I made recently to test the effects of nitrites on the diameter of the radial artery. At 12.15 p.m. my pulse being 66, and the radial diameter in the recumbent position 1·0 mm., I took, after making these observations, at 12.20 one compound trinitrine tabloid containing trinitrine and nitrite of amyl. A few minutes later there was a feeling of general pulsation, the radial diameter in the same position was ·9 mm. At 12.28 it was also ·9, but at 12.33 it had increased to 1·1 mm. larger than it was before the drug was taken, and at 12.40 it was 1·0 again, exactly the same as at 12.15. At 12.28 and with the general throbbing the pulse rose to 76, at 12.33 it was 72, and at 12.40 the same. My notes also show that between 12.28 and 12.33 there were numerous well-marked intermissions of the pulse which were not present at the observations preceding or following these. It seems to me that we have here an instance in which the nitrites which so markedly lower blood pressure, as shown both by the sphygmograph and the arteriometer, and which therefore act just like chloroform, did also like chloroform cause very marked fluttering and irregularity of the heart's action as their effect was passing off and the normal blood pressure was returning.

We see also in this record that the pulse which, in accordance with Marey's law, quickened to 76 when the blood pressure was reduced, remained at 72 when the pressure had again risen higher than before; and we have here again another sign of some failure on the part of the heart, for I have pointed out that the most marked exception to Marey's law is found in the case of a heart that fails and dilates before high blood pressure, as it then quickens with rising pressure in place of slowing down, and my heart in this experiment had been somewhat bothered by the rising pressure at 12.33, as shown by irregular action, and therefore remained quicker than it was before the experiment, in spite of the blood pressure having risen to a greater height.

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The same thing is often well seen in cases of chronic Bright's disease. Here if we get high blood pressure, and the heart's action is slow (*i.e.*, at or below 60), we have to do with a strong heart, which is not failing, or more correctly, has hypertrophied and become equal to its work; in proof of this we get no dropsy of any sort, and the urine is fairly profuse and of low specific gravity, and if we clear the blood of uric acid and free the capillaries, the heart quickens its rate up to normal or above it.

On the other hand, if we have a case of chronic Bright's disease in which the heart is failing, we have the signs of high pressure in the pulse and the second sound at the aortic base, but the heart may be beating from 80 to 120, and probably fluttering or palpitating as well; here we have heart failure, and its results are generally pretty evident in the shape of general dropsy, ascites, congested liver, scanty urine of fairly good specific gravity, in spite of the fact that at the *post-mortem* the kidneys are found to be as fibrous and granular as any you have ever seen. In this case if you can succeed in freeing the capillaries and strengthening the heart it will slow down towards the normal rate of action as the conditions improve.

I have often noticed similar effects on my own pulse produced by taking nitrites, and have no doubt that a similar result could be produced with them any day, especially if taken in the morning hours; but in the above instance the arteriometer enabled me to demonstrate with very considerable certainty the exact relation between the blood pressure and the irregular action of the heart.

I would suggest also that we have here possibly a valuable means of testing in any given case whether it will be dangerous to give chloroform, namely, by watching the effects of a nitrite on the heart's action.

If in any given case it is proposed to give chloroform on Wednesday at 11 a.m., give on Tuesday at the same hour (the reasons for this are, I hope, now obvious) a nitrite, and if as its effect is passing off some 10 to 15 minutes after it has been taken, the heart's action shows marked irregularities, that patient has a somewhat weak heart, or an excess of uric acid in the blood, or both, and it may be dangerous to give chloroform.

For it follows from Dr. Kirk's observations, previously quoted, that the effect of chloroform passes off in a few seconds after it is discontinued, and the resulting rise of blood pressure will be both more sudden and more dangerous, while the effect of the nitrite is more gradual and causes only a little irregularity of the heart's action.

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It will be obvious to those who know the way in which uric acid in the blood and urine fluctuates from day to day, that the above test may give no sign and yet on the following day chloroform may be fatal.

I would suggest also that the nitrite should, where possible, be given more than one day before the chloroform, for it may itself give rise to fluctuations in the excretion of uric acid; this, however, is probably only of small importance, and I think it possible that this test may in many cases give useful indications of danger, and when a patient is only seen a few minutes before chloroform is to be given, the nitrite could even then be tried as the heart was being examined.

I have again to thank Dr. W. Rushton Parker, of Kendal, for the interesting suggestion that my explanation of the causation of chloroform syncope by its effects on uric acid and the blood pressure may account for, to quote from his letter, "the immunity of pregnant women from chloroform syncope as compared with the same women in the *post partum* state." "At the Rotunda Hospital, Dublin (where I was obstetric assistant and chloroformist), we administered chloroform for forceps, craniotomy, &c., without the smallest reluctance; but for removal of adherent placenta, or for stitching a torn perinæum, or for anything *post partum* we always felt the risk to be greatly increased."

Dr. Parker considers that this is common experience among obstetricians, and refers to works on midwifery for similar opinions, and I was myself a student at the Rotunda, and can distinctly recollect the feeling with regard to the administration of chloroform to which Dr. Parker refers.

And if this is the case, we have here an instance in which in a few hours and in the same patient the administration of chloroform passes from safety to danger, in absolute correspondence with a very marked increase in the amount of uric acid in the blood and urine, for I have over and over again pointed out (see chapter iv.) that post puerperal collæmia accounts for some physiological and for nearly all the pathological conditions occasionally met with at this stage of a natural function.

The above-mentioned cardiac failure is accompanied by violent struggling or even convulsions on the part of the animal or patient, and we are here brought again into touch with my explanation of the pathology of convulsions from rising blood pressure in the previous chapter (see also previous remarks on the pulse of epilepsy).

When struggling occurs in the course of inhalation it is, I think,

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the practice of anæsthetists to give chloroform more freely for a little, and this is, it appears, the best thing to do, for the trouble is due to failure in the supply of chloroform allowing the blood pressure to rise.

Then if the tension effects of chloroform are due to its action on uric acid, and proportional to the amount of this substance to be met with in the blood, we can again see several facts which admit of easy explanation. Thus it has, I believe, been suggested that there is more trouble with chloroform in London than in Edinburgh, and again we know that gout is common in London and rare in Edinburgh, and there will probably therefore be more uric acid in the former than the latter; similarly, the vegetarian natives of India may have some immunity from chloroform syncope as compared with beef-eating Englishmen, and this carries suggestions as to prevention. (See also Dr. Kirk's experiences above mentioned as to results in cats and dogs on the one hand, and rabbits on the other, and I am indebted to my friend, Dr. E. G. Horder, for the information that the vegetarian natives of China have a similar immunity from chloroform syncope.)

I am aware that it was suggested in an annotation in the *Lancet* (1889, vol. ii., p. 606), that gout might account for the different reaction to chloroform in Edinburgh, London and India respectively, but no explanation was given of the way in which it acted.

I have already (chapter v.) quoted from Marey the fact that alcohol causes a dicrotic pulse, except when it is accompanied by gastric disturbance; and the said gastric disturbance, by keeping up the alkalinity, prevents the alcohol clearing the blood of uric acid.

I think also that the alcohol or morphine, which are so often advised to be given before inhalation of chloroform, may act by clearing the blood of uric acid, and thus preventing a rebound when the anæsthetic is left off. If there is no uric acid in the blood when the chloroform is given there will be no great change of blood pressure either when it is begun, or when it is left off.

The rebound after alcohol or morphine comes more gradually, and will therefore affect the heart less severely, as is the case with nitrites, but we know that they all do affect it to some extent.

Then, in an interesting address, Dr. Lauder Brunton remarks that he has been told by Professor Poehl, of St. Petersburgh, that in Russia the presence of an excess of alkaloidal substances in the urine is regarded as a sign that it will be dangerous to give chloroform (*Lancet*, 1893, vol. ii., p. 861), and mentions that he himself

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had previously entertained the idea that certain alterations in tissue change might increase the danger of chloroform.

There can, I think, be no doubt that an excess of uric acid in the blood produces very great alterations in tissue change, and we have had a well-marked instance in this chapter in the causation of fatigue. I would also just mention in this connection, a case reported in the *British Medical Journal* (1894, vol. i., p. 1180), in which cretinism was said to follow on depression and worry in the mother during pregnancy, as we may here again have alterations in tissue change due to uric acid, and I suspect that the excess of alkaloids noticed by the Russian observers runs parallel with an excess of uric acid (see chapters viii. and x. to xiv.).

I have often been struck with the fact that the conditions in which increased toxicity of the urine is described are very frequently conditions in which my experience tells me that there must also be an increase of uric acid in the blood and urine; and I would suggest that the quantity both of uric acid in relation to urea and of alkaloids should in future be observed in the urine before operations under chloroform.

Thus after pneumonia and also after typhoid fever the toxicity of the urine is said to be high (*Prog. Med.*, April, 1889, pp. 277 and 296), and after both there is an excessive excretion of uric acid, and all the signs of its excess in the blood. And what I have said about menstruation, and figs. 30 and 31, explains perhaps a case in which chloroform produced a fatal result in a menstruating woman (*Lancet*, 1895, vol. i., p. 237).

As to the way in which an excess of uric acid in the blood may produce these alkaloids, see as regards the intestines, chapter vii., and the causation of oxaluria, chapter xii., and I think there can be very little doubt that a deficient circulation produces a similar effect in the tissues generally. Now Professor Mosso tells us, with regard to the pathology of fatigue, that when it is carried beyond a moderate amount the blood is subject to a decomposing process through the infiltration of poisonous substances into it (see *Lancet*, 1887, vol. i., p. 1295). There is, I think, no doubt that the blood in fatigue contains an excess of uric acid, and owing to the effects of this on metabolism, other poisons (sulphuretted hydrogen, &c.) will soon be added, though I think that uric acid itself either directly or by its effects on the metabolism and combustion causes the decomposition of the blood both in fatigue and hæmoglobinuria (see also chapter xii.).

Another writer tells us that the proportion of alkaloids in the

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urine during the eight hours after waking is five times as great as in the urine of the rest of the day (*British Medical Journal*, 1886, vol. ii., p. 1271.) Now the largest excretion of uric acid and the most marked collæmia occur in these same hours (see fig. 3).

Diagnosis of mental depression due to uric acid depends chiefly on the fact that it is proportional to the uric acid in the blood and fluctuates with it; that, as pointed out by Professor Lange, it is periodical, in which also it resembles the headache and fits due to the same cause. Being directly due to the high blood pressure which uric acid produces, it is made worse by anything which raises blood pressure, and better by anything which reduces it.

Undue fatigue, again, is to be recognised from its fluctuating in accordance with the amount of available uric acid, and this can be actually demonstrated as in figs. 39 to 42.

It will readily be understood that this pathology leads one to form a favourable prognosis both in mental depression and slight melancholia; control the uric acid and you have controlled the mental disease. The anatomical factor (large arteries of supply to the brain), far from being a drawback is an actual advantage to the race; supply these arteries with pure blood, and in place of pathological deviations, you have a brain with more than the ordinary physiological powers. Here probably is the explanation of the observation frequently made, that the step from great mental power to insanity often seems a short one; for the anatomical conditions which make great mental power possible, also make it possible for the brain to be seriously affected by impure blood and high blood pressure.

The indications for treatment are practically the same as those for the collæmia of headache, bearing in mind that collæmia which produces mental depression is very often secondary to other conditions, such as dyspepsia, debility after parturition, prolonged lactation, or fevers, or accompanying the progress of new growths or other organic disease; and it is useless to treat the collæmia without paying attention to its cause, though in any case a diet which diminishes the intake of urates will probably do some good, for the more the available urate the greater and more lasting, as we have seen, is the interference with metabolism and nutrition.

A craving for animal food at an early age in children is by some regarded as a sign of impending insanity; and it is said that children naturally do not crave for it (see *Lancet*, 1896, vol. ii., Dr. McNeill); and some similar remarks have I believe been made by Dr. Clouston, and these interested me because I have often noticed

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a similar craving for meat in epileptics, and to my mind such unnatural craving is often due to the temporary relief which eating meat affords to the high blood pressure of collæmia, and its mental and physical results.

I think that our knowledge of the causation of fatigue thus obtained may come to be of great use to our soldiers and sailors, or any men in similar positions who may be suddenly called upon to make enormous exertions on which their safety and that of others may depend. It also completely explains the well-known use of opium by the natives of India, to enable them to perform great feats of strength and endurance.

The most powerful man would be of little use in a fight, if he had eaten so much dinner that there was no room for his heart and diaphragm to work; similarly the man who at the first brush of fighting gets his blood loaded with uric acid, and in consequence has the circulation through his muscles so much obstructed that waste products are but slowly removed, while his heart fails and dilates before the rising blood pressure, will soon be overcome by a better trained and more nimble antagonist.

Now this man fails not because his muscles are wanting in size and power, and not because they are worked out, but simply because, owing to defective circulation, they are clogged with waste products, acting as I have said above, like a wet blanket on the kitchen fire.

The fall of urea which exercise produces is the measure of this clogging with waste products, and as we have seen, the more the uric acid in the blood the more the fall of urea and the more the clogging. The rise of urea next day represents the washing out of these waste products when the circulation through the muscles is again freed from uric acid.

And clearing the blood of uric acid does instead of training, and by freeing the circulation through the muscles allows of an immediate removal of waste products, as shown by an immediate rise of urea, in place of a fall, and while this lasts there is no fatigue, and the muscles are capable of comparatively unlimited activity.

Now the power to produce this condition when wanted may often make all the difference between defeat and victory, and if muscle power is good, almost puts an untrained man on a par with a trained one.

I believe also that in the course of the year there are not a few cases in which otherwise good lives are lost owing to heart failure

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and syncope before the high blood pressure which fatigue induces; and that a timely use of opium, mercury, or any other drug that will keep the blood clear of uric acid, might suffice to save them.

I am indebted to Dr. W. R. Edwards, of Quetta, for the interesting information that some of the native horsemen of India are in the habit of giving opium to their horses after a hard day's work, and they say that if they do not the horse will not sleep, will go off its food, and be useless next day; but if opium is given it will sleep, and take its food, and be all right next day.

Here, then, we have in horses exactly what occurs in man, fatigue causing collæmia, high blood pressure, and sleeplessness; but if the capillaries are freed and the blood pressure lowered by opium or mercury (see previous remarks, p. 250), sleep comes naturally, and all is well next day. We must also bear in mind in considering this result the effect of a free capillary circulation on the nutrition of the muscles. I have also already referred to the fact that horses suffer severely from rheumatism which is in some respects but a mere exaggeration of fatigue and stiffness.

It would be worth considering also whether the evil effects of heat are not, to a large extent, the result of the collæmia it occasions, and whether the use of drugs which keep the blood clear of uric acid would not diminish them; and indeed the use of opium by the natives of India almost amounts to proof that this is so.

In my own case the previous clearing out of uric acid by a course of salicylates completely prevents—at least for some hours—the usual depressing effects of exposure to heat and exertion.

When the day of exertion is known some time beforehand, the salicylates can be used as in fig. 42, but the more useful and immediately available method is to employ a drug which directly interferes with the solubility of uric acid in the blood, especially a metal like mercury, which forms an insoluble compound with it, and such a drug can be carried in the pocket and taken as required just before and during the exercise.

The action of these last-named drugs, unlike the salicylates, will be followed by a rebound when they have been left off for a few hours; but this will probably do no harm, and is but a small price to pay for winning a victory, or saving a life from syncope.

Where syncope occurs at such hours or under such conditions as suggest a relation to possible excess of uric acid in the blood, the power of drugs or diet in keeping it clear should not be forgotten.

The use of chloroform as an anæsthetic seems to be contra-indicated by the presence of headache (migraine), mental depression,

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fits, high blood pressure, Bright's disease or albuminuria, diabetes or glycosuria, and of fatigue or menstruation, in physiology; though in all these cases its effects will depend upon whether the heart is quite strong, or is beginning to fail before the high blood pressure, in this last named condition it may be most dangerous.

I must point out also that the effect of a uric acid free diet on my own strength and power of endurance has been enormous; words quite fail me to give an idea of it, and only those who experience it in themselves can fully understand what I mean.

I believe that I do not exaggerate when I say that the effect of getting free from uric acid has been to make my bodily powers quite as great as they were fifteen years ago, indeed, I scarcely believe that even fifteen years ago I could have undertaken the exertion I now indulge in with absolute impunity; with freedom from fatigue and distress at the time, and immunity from stiffness next day. Over and over again this spring I have got up from a week or more of the most absolutely sedentary work and ridden on a bicycle fifty, sixty, seventy, or even eighty miles, without any fatigue other than a little soreness from the unaccustomed saddle, have been able for ordinary work the rest of the day, and next day quite fit to do the same again if necessary.

Now my recollection of meat-eating times is that I could do nothing of this kind, especially in spring (the first warmth of the year), and when out of training; then, especially if the wind was warm and perhaps moist, one and a-half or two hours' work would find me in a position of considerable distress from fatigue, making a rest imperative. Now heat and moisture do not affect me unless, perhaps, they make me better able for work, but the old feeling of absolute inability to proceed is quite unknown. Indeed, I often say that it is now impossible to tire me, and relatively I believe this is true. I have already referred to the fact that heat does not affect those who have cleared the blood of uric acid by means of salicylates, and we now see that the same holds when it is cleared by diet.

So that we have here again the most unmistakeable evidence that uric acid is not only the cause of many dangerous and painful diseases, but also in the domain of physiology accounts for much defective circulation and nutrition with the corresponding defects in function, in strength, and especially in endurance, and I have already referred to the recent frequent remarks in the daily papers on the magnificent physique and powers of endurance of the vegetarian Turks.

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I am also indebted to Dr. W. R. Edwards for the information that though he could probably tire out a native of India on one day, the next day the native is all right and could do the same again, while he, Dr. Edwards, is stiff and sore, and not fit for much for several days.

My impression is that few meat eaters of my own age would tire me out, and the above record raises in my mind a doubt whether the native in question had a sufficient supply of nitrogen (see chapter xvii.).

It is now also getting to be common knowledge among athletes that meat is not the best food for them to train upon, and some of the more advanced among them, as Mr. E. H. Miles, of Cambridge, who recently won the tennis championship, have altogether abandoned it; and the facts and experiments recorded in this chapter suffice to explain their experiences.

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CHAPTER IX.

Asthma and Bronchitis.

Before I attack the special subjects of this chapter I will say a few words about what is called a common cold. My point with regard to it is this—how far is a common cold due to changes originating within the body, how far is it due to external agencies?

We all know that a cold may run through a whole house; in this case in so far as B's cold was due to proximity and contact with A, it was due to agencies entirely external to his (B's) body. But there are obviously other factors, for B does not always get A's colds; on the contrary, it is only when he is a little out of sorts, when he suffers from dyspepsia, or other small causes of trouble, that he is liable to get them; at other times when he is in perfect health he may entirely escape.

Again, it is common experience that women are specially liable to take cold at their menstrual period, when they are also more liable to dyspepsia, gastric upset, bilious attacks, &c.

It is, I think, therefore evident that in a common cold we have two factors, (1) altogether external to the body, and (2) originating in certain disturbed conditions of digestion, nutrition, and metabolism inside the body. If 1 does not coincide with 2 no disease results.

The meteorologists who take charge of the observatory on Ben Nevis have given us (*British Medical Journal*, 1895, vol. i., p. 248) an extremely interesting account of their experiences with what they call the Ben Nevis cold. It appears that they get this cold about forty-eight hours after they come down from the observatory; they have no colds while at the top of the mountain, and if they go up with a cold it promptly takes its departure.

Now, this is very interesting, for there is no doubt about the infection, they go up to the top of the mountain with a cold, and it quickly comes to an end and does not spread to others; again, they come down from the mountain without a cold and very often get

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one. In this latter case they are exactly in the condition of a woman during menstruation; while they are up on the mountain they are braced up by the cold, *i.e.*, the blood is cleared of uric acid by the falling alkalinity which the cold produces, hence as we have seen in the last chapter, the fires of life will burn strongly and brightly, and the microbes will have no chance. But where is the uric acid that is not in the blood? it is held back and retained in the various organs and tissues, and as soon as they descend to the more relaxing climate of the low country, the alkalinity of the blood rises, and all this uric acid is got into solution and passes through it; they are now exactly in the condition of a woman during menstruation (see figs. 30 and 31), and are liable to take a cold whenever exposed to its microbes.

We see exactly the same thing with regard to other bracing climates as the Engadine; if any one goes there with a cold it is soon thrown off, and while there they either do not get cold, or if they do it comes to nothing. "The Ben Nevis cold" is really a misnomer and a slander on the mountain, for Ben Nevis really protects them from cold; but it does this by storing up a certain amount of uric acid which, when they again descend, will pass through their blood and render them more than usually liable to take cold.

In accordance with this Dr. Solly tells us (*Medical Climatology*, Philadelphia and New York, 1897, p. 39) that cold increases muscular power, and again (p. 66), that dry cold air is stimulating when the temperature is not too low: that is to say, a very low temperature may put out the fires of life, but short of this it makes them burn up more brightly by putting an end to collæmia and producing a free capillary circulation. This author also tells us on p. 164 that just as we should expect, the first effect of high altitude upon both migraine and epilepsy is beneficial; and with regard to the latter he says, "the strong tonic and alterative qualities of altitude are often of the greatest service," and as we know the patient will be kept relatively free from collæmia as long as the "tonic" effects continue; but after that he will relapse.

Then, again, I think it must be common experience that a cold is often greatly improved, or if treated early even cured, by a good purge. In a word, I believe that the internal condition which allows the external factor to act is often some intestinal condition which is put right by a purge. Similarly, a dose of wine negus, or of spiritus ammon. aromat., and sp. æther nit., or of pulv. ipecac. co., at bedtime, have cured or cut short many a cold. They all

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clear the blood of uric acid, and free the capillaries throughout the body; quickening metabolism and combustion.

Such is, I believe, the origin of all colds; a predisposing condition produced by collæmia, viz., a damping down of the fires of life, plus a microbe; and this predisposing factor is probably common to a large number of infectious diseases, such as phthisis and the exanthemata, and explains the fact that a man may be exposed to a disease many times without taking it, and yet eventually take it when it catches him some day in a state of defective combustion. We see, I think, also the same thing in children, who come to the out-patient room one week with diarrhœa, and the next with bronchitis; and it is almost never the other way. Here obviously the diarrhœa will cause collæmia and the collæmia will render them liable to catarrh; again, teething and the gastro-intestinal disturbances it produces, will predispose to catarrh so that some children have bronchitis with each set of teeth they cut.

I hope that in what I have to say about bronchitis and asthma we may get an insight into the nature of some of these internal conditions, and the way in which they may favour the onset of a common cold.

Several years ago, in a paper in "Wood's Medical and Surgical Monographs" (New York, February, 1890, p. 359), I said with regard to asthma: "Here, again, we have a possibly functional disorder which, like so many I have mentioned, has long borne a somewhat indefinite relation to gout, and it has occurred to me since my investigation on uric acid has brought to my notice its action on the capillaries, that directly or indirectly it may affect the circulation in the bronchi and lungs and so produce asthma. There are also not a few points in the history and symptoms of asthma, and the onset of the attack, which may be taken as pointing to its possible origin in a uric acid storm."

I have also mentioned elsewhere several things which seem to make it probable that uric acid affects both the pulmonary and the systemic circulation in the same way.

My interest in the matter was also greatly quickened by seeing in the *Lancet*[1] a notice of a paper by Dr. Yavein, of St. Petersburg, in which it appeared that large doses of citrate and carbonate of soda diminished the excretion of water from the skin and lungs, for I already knew that similar doses of these alkaline salts would, by increasing the uric acid in the blood, obstruct the vessels in the

[1] *Lancet*, 1892, vol. i., pp. 329 and 882.

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kidneys, and diminish, so long as the excess of uric acid might last, the excretion of water in the urine.

It seemed probable, then, from these considerations that uric acid not only affected, as I already knew well, the vessels of the kidneys and skin, but Dr. Yavein's results made it probable that it affected also the vessels of the lungs and diminished the output of water from them, and as soon as I was able I began some researches with a view to confirm Dr. Yavein's results, of which I shall speak presently.

Asthma is commonly spoken of as a paroxysmal affection, attacks coming suddenly about 2 a.m. to 4 a.m., when the sufferer has gone to bed quite well. The dyspnœa is expiratory, and is supposed to depend on a morbid condition of the very small bronchial tubes; and this morbid condition is supposed to consist of hyperæmia or congestion, with or without the addition of a certain amount of muscular spasmodic constriction.

Now, asthma has been called by Dr. Goodhart[1] and others a "paroxysmal neurosis," and they would, I suppose, probably class migraine and epilepsy in the same category; but I have shown[2] that many cases of migraine and epilepsy are entirely due to the changes which uric acid produces in the circulation of the nerve centres, and that if the blood is kept clear of this poison the attacks will practically cease to recur.

And my researches leave little or no doubt in my mind that asthma represents one of the effects of uric acid on the circulation in the thorax, and that it is paroxysmal for the same reason that migraine and epilepsy are paroxysmal in accordance with the natural fluctuations in the excretion of uric acid, and the amount of the substance passing through the blood; and we shall see further on that clearing the blood of uric acid and keeping it clear is the only point requiring attention in the treatment of asthma, and that all drugs which experience has shown to be useful in this disorder have this effect, or else directly reduce the high blood pressure which uric acid produces, and further, they are almost all equally useful in migraine and epilepsy.

We now come more directly to the relationship of the asthma attack to the excretion of uric acid.

And one of the first things which directed my attention to this matter was the very similar effects of diet both in migraine and

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[1] *British Medical Journal*, 1891, vol. ii., p. 254.

[2] *Brain*, Spring and Summer Number, 1893, p. 230.

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asthma. It will be remembered that I was myself a sufferer from migraine, that when I was on ordinary meat diet I used to have about 30—40 attacks in a year, that when I was on extra meat diet for purposes of training at Oxford (and it now appears to me that this was indeed a very dangerous process) my attacks were both more frequent and severe, while now, when I take no meat at all, they are practically absent altogether; and I therefore learned with great interest from one of my fellow students (the late Dr. W. E. Steavenson) that his asthma attacks had been affected in exactly the same way by the training he had done at Cambridge. He suffered also from eczema and bad headaches, and had had acute rheumatism, and his pulse was often slow and of high tension.

Then I have myself had attacks which, if not strictly asthmatic, are undoubtedly closely related to it, and before I recognised this relationship they used to cause considerable uneasiness in my mind by suggesting more serious disease.

Thus I noticed that occasionally in the early morning before breakfast I had a feeling of heaviness or tension behind the sternum, with a little wheezing in the chest, followed by the expectoration of a little mucus; I also noticed that the pain invariably disappeared soon after breakfast, though both the pain and wheezing occasionally returned about 5 or 6 p.m., to disappear again after dinner.

What specially struck me was the comparative suddenness with which the pain came and went, and the fact that there were no signs of catarrh whatever at other times of the day.

Some time after this, in the course of an experiment undertaken for other purposes, I purposely increased very greatly the excretion of uric acid and the amount passing through the blood; and I found rather to my surprise that my chest pain and troubles were very decidedly worse during this experiment, and when, later on, I reversed the process and cleared the blood of uric acid, so that there was but a very small excretion for several days, my chest troubles completely and suddenly disappeared and remained absent for some time, till one or two meat and wine dinners with friends increased the uric acid once more and brought back a morning wheeze.

This opened my eyes to the real nature of my trouble, and I was at once able to explain its periodicity; for, as I have pointed out, the largest excretion of uric acid occurs in the early morning hours before breakfast, and the next largest in what I have spoken of as the afternoon alkaline tide, from 3 to 6 p.m.

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Again, the onset of the attack in the early morning hours, just when the acid tide of the night is coming to an end, and the excretion of uric acid is rising (figs. 2 and 3), the fact that it tends to be better in winter, when, as I have shown, the excretion of the uric acid is low, and worse in the spring and summer,[1] when the excretion is high and rising (fig. 4), are points in which it resembles migraine, mental depression, and other troubles due to uric acid.

Asthma, again, tends to be better during pregnancy unless there is much vomiting, and this is easy to explain, for pregnancy entails a general increase of metabolic activity, which results in a rise of urea, and a corresponding rise in the acidity of the urine and a correlative fall in the alkalinity of the blood, which is now no longer a good solvent of uric acid, so that it contains but little of it; it is easy to understand, on the other hand, how vomiting will reduce urea and acidity, increase the alkalinity of the blood, and flood it with uric acid.

In this relation to pregnancy asthma is the exact parallel of migraine, epilepsy and Raynaud's disease, for all these kindred troubles are better or cease during normal pregnancy, but return when it is over.

I have been told by several sufferers, among others by the late Dr. Steavenson, that the asthma attack is often followed by a diuresis. Here again the parallel with migraine, epilepsy and Raynaud's disease is absolute; and this fact proves to my mind not only that the capillaries are free after the attack with a low excretion of uric acid in the urine, but also that they were obstructed during the attack, causing a retention of water in the body, which takes the first opportunity of passing off as soon as they are again free at the end of the attack.

But I have shown that the urinary water is from day to day and hour to hour inversely as the uric acid excreted along with it, *i.e.*, with high uric acid you get low water, and *vice versâ*. The excess of uric acid in the urine is the index of a similar excess in the blood, and the excess of uric acid in the blood obstructs the capillaries all over the body, among others, those of the kidneys, preventing the outflow of water (see *Journal of Physiology*, vol. xiii., and article on "The Elimination of Water and the Pathology of Dropsy" *Lancet*, July, 1892).

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[1] See *Progrès Médical*, January, 1890, p. 73.

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The fact, then, that the attack of asthma is followed by a diuresis proves, just as in the case of headache, epilepsy and Raynaud's disease, that the attack was accompanied by a plus excretion of uric acid, with high blood pressure and scanty urine.

There can, then, I think, be no doubt about the relationship of the asthma attacks to a large excretion of uric acid in the urine, or to the high blood pressure which its excess in the blood produces, and we shall see other reasons for this opinion further on.

With regard to the researches of Dr. Yavein, showing that alkalies diminish the output of water from the lungs, I have made some experiments, comparing the excretion of water from the kidneys with that from the lungs in a given time.

I knew that I could control the excretion of water from the kidneys by acting on the uric acid in the blood, and increasing or diminishing its quantity; and I argued that if alkalies which diminish the urinary water by increasing the uric acid in the blood, diminish also the excretion of water from the lungs, then I ought to be able to control the excretion of water from the lungs as well as that from the kidneys, and my researches, so far as they go, seem to show that, to a certain extent, this is the case.

I began to investigate the matter in the following way: I measured the urine passed in 15 minutes, and estimated by means of tubes filled with calcium chloride the water from the lungs in 5 minutes, generally in the middle of the 15 minutes in which I estimated the urine; I then divided the urine passed in 15 minutes by 3, and compared this with the water given off in 5 minutes from the lungs (see chapter xviii.)

I followed first of all the natural fluctuations in the urinary water, and then proceeded to produce fluctuations by means of drugs affecting the uric acid.

In Carpenter's "Physiology," ed. viii., p. 482, it is stated that from 7—11 oz. of water is daily thrown off from the lungs, the exhaled air being saturated with water, or nearly so. The quantity varies with the rapidity of respiration, with the stage of digestion, and rest or activity, &c.

Taking the quantity as 11 oz., and the urine as 52 oz., we get a relation of 1 part of water from the lungs to 4·7 parts from the kidneys.

The results I shall now mention were obtained generally about the same hour of the day and at rest, so as to eliminate as far as possible the effects of digestion and of exercise.

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Date. 1896.			In five minutes. Water from Lungs. grams.		Water from Kidneys. cc.		Relation.
Feb.	1	..	1·169	..	4·5	..	1-4·8
„	2	..	1·497	..	7·0	..	1-4·6
„	3	..	1·514	..	6·0	..	1-3·9
„	4	..	1·560	..	6·1	..	1-3·9
„	8	..	1·670	..	7·3	..	1-4·3
„	10	..	1.367	..	6·0	..	1-4·3
„	17	..	1·310	..	5·6	..	1-4·2
„	18	..	1·466	..	6·3	..	1-4·2
„	18[1]	..	1·515	..	7·6	..	1-5·0
May	10	..	1·186	..	4·6	..	1-4.1
June	8	..	1·190	..	4.3	..	1-3·9
„	9	..	1·370	..	4.3	..	1-3·1
		Total	16·814	..	69·6	..	1-4·1

[1] Two consecutive experiments.

I also made similar experiments on ten other days at times when the urine was very profuse, as from 10—18 cc. in the 5 minutes, and in none of these did the water from the lungs rise to a corresponding extent, probably because the expired air was saturated and no more water could therefore be given off by the lungs; and on these days one got relations of 1—10, 1—12, and even 1—14. That is to say, for obvious physical reasons, the water expired from the lungs cannot rise beyond a certain point.

From the figures given in the above table it is seen that the total excretion from the lungs was 16·8 grams, and from the kidneys 69·6 cc., giving a relation of 1—4·1, a difference of six points in the first place of decimals from the relation obtained from the above quoted work on physiology. If in the same table we take the highest excretion from the lungs, 1·67 grams, the corresponding excretion from the kidney is 7·3 cc., the lowest from the lungs is 1·16, and the corresponding kidney excretion 4·5 cc. Then the highest excretion from the kidney is 7·6 cc., and the corresponding excretion from the lung 1·5 gram; the lowest from the kidney is 4·3 cc., and the corresponding excretion from the lung 1·1 gram.

Thus it appears that within the limits imposed by the physical laws which govern the saturation of the atmosphere with moisture, the excretion of water from the lungs does vary on parallel lines with excretion of water from the kidneys with a relation of 1—4·1 to 1—4·7, and those things that increase the excretion of water from the kidneys will also increase the excretion of water from the lungs within these limits.

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I have also made similar experiments with opium, mercury, nitrites and other things which clear the blood of uric acid, and find that when these increase the urine they at the same time increase the excretion of water from the lungs.

My research, then, seems to show that Dr. Yavein's observation was quite correct, and that an alkali which diminishes the water from the kidneys (see p. 163) so long as it increases (*but only so long*) the uric acid in the blood and urine, will at the same time diminish the excretion of water from the lungs to a corresponding extent.

Having found, then, that the water exhaled from the lungs varies with the water excreted from the kidneys within certain limits, we must consider the probable cause of this parallelism of the two excretions.

I have said above that in everyone from hour to hour and from day to day the excretion of water from the kidney varies in the reverse direction with the excretion of uric acid; and so constant is this law, that by controlling the excretion of uric acid I can control the water with a certainty that is little short of absolute; and in clinical work if the water is known from day to day, the uric acid, greater or less, can be calculated from it with considerable certainty (see *Lancet*, July, 1892, and elsewhere); and not only so, but all the important drugs (mercury, opium, salicylates, iodides, caffeine, &c.) which cause diuresis, do as I have shown, diminish the excretion of the uric acid at the time of the diuresis, or, as I put it, they cause a diuresis by clearing uric acid out of the blood and enabling the vessels of the kidney to dilate, because the obstruction of the capillaries throughout the body varies directly with the amount of uric acid that is circulating in the blood (see *British Medical Journal*, February, 1889).

But in the uric acid headache, and other conditions in which there is an excess of uric acid in the blood, not only is the urine scanty and the skin pale, cold and dry, but the saliva also is scanty, and it can be shown (*Brain*, 1893, prev. ref. and ch. x.) that the gastric juice, the bile and the intestinal juices are all equally scanty, and we now see that there is some reason to believe that the excretion of water from the lungs is correspondingly diminished.

And the explanation of this is simple, for the capillaries throughout the body are all obstructed by the uric acid in the blood (collæmia), and if the blood is examined at this time it will be found to contain an excess of water, both hæmoglobin and cells being relatively diminished.

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We have arrived then at this point that uric acid which obstructs the capillaries throughout the entire systemic circulation, and diminishes all the excretions, affects also the vessels of the lungs and diminishes the output of water from them to a corresponding extent.

What is the bearing of these facts on the pathology of asthma, a paroxysmal disturbance of function resembling at so many points, as I have shown, migraine and epilepsy and Raynaud's disease, which are also paroxysmal?

As I have said, I think it can be shown that migraine, epilepsy and Raynaud's disease are paroxysmal in relation to the fluctuations in the excretion of uric acid and the amount of it that is passing through the blood, migraine and epilepsy representing the affects of high blood pressure on the intracranial circulation, and Raynaud's disease the effects of obstructed capillaries on the nutrition of the skin and extremities (chapter xi.).

Asthma appears to be paroxysmal in relation to similar fluctuations of uric acid; is it one of the effects of uric acid on the pulmonary circulation?

Now let us look at one or two points in the anatomy and physiology of the lungs.

We have two circulations going on there, (1) that of the pulmonary artery in which there is comparatively low pressure, and (2) that of the bronchial arteries which come from the systemic circulation, in which there is much higher pressure; and we have these circulations enclosed in a cavity, the pressure in which varies greatly from moment to moment with respiration.

But if you diminish the atmospheric pressure on any vascular area of the body, its capillary vessels at once dilate (see Marey, "La Circulation du Sang," 1881, p. 444), and it seems obvious that most blood will stream into that area which has the highest blood pressure behind it, because it is the pressure in the arteries which drives the blood through the capillaries into the veins (see Marey, p. 321, *et seq.*). It follows from this reasoning that when atmospheric pressure is diminished in the thorax, there will be more congestion in the bronchial circulation than in the pulmonary; and there will be more congestion in the bronchial circulation the higher the blood pressure in the systemic circulation of which it forms a part.

Here, then, we have a tendency to hyperæmia and congestion in the lungs, which is probably most marked in the area of distribution of the bronchial arteries, which will increase on the one hand

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with rising blood pressure, and on the other with anything that obstructs the free entry of air in the thorax, and so tends to diminish more than usually the atmospheric pressure during inspiration.

It is interesting to note that Marey (prev. ref., p. 448) attributes in no small degree to the diminished pressure in which they have to work, the ease with which the lungs become congested or inflamed.

It seems to me that such a congestion or hyperæmia affecting especially the bronchial circulation may quite account for the retro-sternal pain, with slight increase of bronchial secretion and wheezing, which I have myself experienced in connection with excess of uric acid in the blood, and the high blood pressure it produces; and a slight increase of this disturbance may easily account for the bronchial congestion of asthma.

May not something of this kind represent the internal factor in the causation of a common cold, and explain its relation to dyspepsia, menstruation, &c., which, as we know, so often upset the physiological balance, and bring an excess of uric acid through the blood, producing high blood pressure, and, in the way just explained, hyperæmia or congestion in the area of the bronchial circulation in the thorax?

Do we not here also get a ray of light on the causation of chronic bronchitis, and on its frequent association with chronic Bright's disease and high blood pressure in the declining years of life? Bronchitis also is common at the two ends of life, and in both of these we get excess of uric acid, excessive formation in children and excessive excretion in the old.

It is exactly in the declining years of life that owing to failing nutrition, falling urea, and diminishing acidity we get a very large amount of uric acid dissolved out and passing through the blood, and most in those who have taken most freely a highly nitrogenous diet in the previous twenty or thirty years of their life.

The collæmia thus brought about obstructs the capillaries and raises blood pressure, and the further general failure of nutrition, the chronic Bright's disease, and the chronic bronchitis, are secondary to this; it is little wonder, then, that as pointed out by the late Professor Humphry, a large proportion of those who attain to great age are more or less strict vegetarians.

It seems probable that once this bronchial hyperæmia has come into existence the swelling of the mucous membrane may further obstruct the passage of air to the bronchi and alveoli on the distal

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side of this obstruction, and this will lead to continually increasing fluctuations in the pressure in the distal air passages, with increasing hyperæmia and congestion, so that matters tend to get worse and worse, and the hyperæmia only subsides after it has been relieved by a copious secretion of mucus or a general oozing of blood.

I do not think that an affection of the bronchial area alone will account for the fluctuations in expired water which take place, and believe that uric acid will affect the pulmonary vessels as well as the bronchial, and may possibly do this to the extent of greatly obstructing its vessels and rendering the whole lung anæmic; but this is probably a rare condition of affairs, though occurring perhaps in uræmia or other organic disease, and the more common effect of collæmia and high blood pressure is the congestion and hyperæmia in the area of distribution of the bronchial arteries, which I have endeavoured to point out above, and which, when slight and chronic, may lie at the root of chronic bronchitis or the onset of cold, but when more sudden and severe may produce an asthmatic paroxysm.

If asthma has a causation such as I am suggesting, it will be made worse by anything that obstructs the capillaries and raises blood pressure, and it will be made better by anything that frees the capillaries and lowers blood pressure. It will also be made worse by anything that obstructs the free entry of air into the thorax.

The most common cause of high blood pressure is uric acid in the blood, and this suffices to explain at once the relationship of asthma to gout and various other diseases, as we shall see.

The relationship of the asthmatic attack to the early morning hours is simply its relation to the largest excretion of uric acid in the twenty-four hours, and the change about 4 a.m. from a free circulation to an obstructed one (fig. 2), and asthma at this point parallels very closely the causation of angina.

During sleep also the patient is generally in the recumbent position, and this position raises the general arterial tension as compared with sitting or standing (*Marey*, prev. ref., p. 349), hence a sufferer can sometimes sleep in a chair but not in a bed; though no doubt also position affects the action of the muscles of respiration.

I have spoken above of the relationship of asthma to diet, and this is quite easily explained by its effects on the uric acid in the blood, and not a few of the minor premonitory symptoms of an attack are those of collæmia.

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No one who understands the relationship of dyspepsia to migraine and epilepsy will have any difficulty in understanding its relationship to asthma. In all cases, however, the relationship is a double one. Dyspepsia is partly a cause and partly an effect, of collæmia and high blood pressure.

There can be no doubt that collæmia when it obstructs the capillaries may practically suspend entirely gastro-intestinal digestion and absorption, and allow putrefactive processes to take their place; in this way collæmia causes dyspepsia (see chapter x.).

But dyspepsia, on the other hand, will also cause or increase collæmia. Suppose there is no excess of uric acid in the blood, but that some indigestible substance as a piece of pork upsets gastric digestion; the result is the more or less complete arrest of digestion and absorption, even if there is no vomiting, and this promptly causes a fall in urea and a corresponding fall in the acidity of the urine; the alkalinity of the blood is increased, and any uric acid within its reach is at once taken up in solution. Such is the usual causation of a "bilious attack," or uric acid storm, and the high blood pressure which results from the passage of the uric acid through the blood produces either headache or epilepsy, or, if the dyspepsia is chronic rather than acute, mental depression, and leads on through chronic obstruction of metabolism and combustion, to that general failure of nutrition which we call Bright's disease.

I believe that the relationship of asthma to dyspepsia is precisely similar, and in some cases the cure of the dyspepsia is the cure of the asthma.

The relationship of asthma to gout is equally simple, and is shared also by migraine, epilepsy and Raynaud's disease.

Asthma is due to uric acid in the blood and the high blood pressure it produces. When from any extraneous cause, as a blow, a chill, a local irritation, or a rise of temperature, uric acid is precipitated on a joint, the blood is cleared of the excess it previously contained, and the high blood pressure and the asthma subside. An interesting case of this kind is mentioned in the *British Medical Journal*, 1888, vol. ii., p. 954, where it is told of Frederick the Great that he had a severe attack of dyspnœa followed next day by gout. It is further said that he was very gouty and had an irascible temper; this last representing the effects of uric acid on the intracranial circulation, just as the dyspnœa represented its effects on the thoracic.

Phthisis and gout are sometimes said to be related (see *Medical Times and Gazette*, 1862, vol. i., p. 499, and *Deutsch. Archiv. f. Klin.*

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Med., b. 47, hft. 5 and 6; also Sir Dyce Duckworth, "A Treatise on Gout," p. 172, where many interesting points are mentioned), and they certainly often occur in the members of the same family, as I have several times remarked. It seems also that they do not both occur at the same time, but alternate, just as asthma and gout do; and I know that this was the opinion of the late Sir Andrew Clark, arrived at, as he himself told me, from personal experience (see also *British Medical Journal*, October, 1889.)

Thus, speaking of his own case on one occasion, the late Sir Andrew Clark said "when I was a young man I had to choose between gout and phthisis, and I chose gout," he evidently thought that by eating a large amount of animal food he was cured of his phthisis and got gout in its place, and his words impressed me very much, because they raised in my mind the fear that in fleeing from gout I might rush into the arms of phthisis, thus reversing his experiences, and it was a discussion on diet with reference to my observations that led him to make the above statement.

There can be little doubt that the late Sir Andrew Clark chose wisely, for though collæmia and high blood pressure eventually caused his death, he had lived for many years an active and useful life, which phthisis would have made impossible.

Now it appears to me that the changes in the pulmonary circulation which uric acid produces may completely account for this antagonism between gout and phthisis. For while a man is eating largely of animal foods, he will have high acidity, his blood will be pretty clear of uric acid, and his pulmonary circulation will be free; but he will have gout, because he is storing and retaining large amounts of uric acid.

Let this man, however, meet with an accident which confines him to bed for weeks and months, so that appetite, digestion and metabolism all run down; with falling acidity the stored urate will pass in excess through his blood, his pulmonary circulation will be more or less markedly deficient, and the bacilli will have their opportunity, and may not neglect it. I believe that such chronic collæmia is a great danger for the lungs.

On the other hand, it may be possible, even after the bacilli have obtained a foothold in the lungs, to burn them up and destroy them by taking a large amount of animal food, which, as we have seen, keeps the blood free from uric acid, and makes the fires of life burn brightly.

Collæmia may also be brought about and kept up by dyspepsia and other gastric troubles, hence perhaps the origin of the dictum

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I have heard at lectures at Brompton Hospital with reference to the treatment of early phthisis, "Take care of the stomach, and the lungs will take care of themselves."

A similar explanation may also apply to the cases of acute phthisis following destruction of the mucous membrane of the stomach by corrosive fluids recently recorded by Dr. Soltau Fenwick (*British Medical Journal*, 1894, vol. i., p. 129).

Phthisis again, like asthma, is often markedly worse in the spring of the year (see Dr. Barlow, *Lancet*, 1891, vol. ii., p. 285, also fig. 4), and iodides are supposed to be useful in cases in which there is a syphilitic taint, but if these drugs keep the blood free from uric acid (fig. 21), and thus allow of a good circulation through the lungs, I should be quite prepared to find that they cure many cases that have nothing to do with syphilis.[1]

But if the observation of the late Sir A. Clark is correct, and is explained as above suggested, we ought soon to be able to escape phthisis and burn up the bacillus of tubercle, without having to reckon later on with the serious effects of collæmia and high blood pressure; for there are plenty of ways of clearing the blood of uric acid and stimulating the fires of life without introducing a large amount of uric acid in the food, which will cause damage in the future. Here again, fever may be nature's mode of defence, and an attempt on her part to burn up the invaders, and we ought obviously to help her in her endeavours by keeping the capillaries as free as possible from uric acid. If the progress of phthisis is thus dependent on the effects of uric acid on the circulation and combustion, we can easily understand the observation recorded by Dr. Barnes in the *Lancet*, 1894, vol. ii., p. 1266, that phthisis makes increased progress from the moment of parturition, it even looks as if, like migraine, epilepsy, asthma, and Raynaud's disease, it is slightly better during normal pregnancy.

Asthma has occasionally been seen to alternate with epilepsy, and this is probably simply due to the fact that some third factor has for a time rendered the thoracic circulation more liable to be upset by the collæmia and high blood pressure than the intracranial; and any temporary interference with free inspiration might, as I have suggested, account for this (see also a case recorded in the *Lancet*, 1893, vol. i., p. 1383).

Then again, the relationship of asthma to eczema and skin

[1] It is interesting to note also that iodides appear to be useful in actinomycosis. (See *British Medical Journal*, 1894, vol. i., p. 61.)

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diseases is probably simple, for I have pointed out in my writings on Raynaud's disease (see chapter xi.) that not a few skin diseases represent merely the effects on its nutrition, of vessels obstructed by uric acid; and I have for several years taken this probability as my guide in the treatment of such skin diseases as come under my notice, with results which have often appeared to me to be very satisfactory.

We must bear in mind that such skin lesions are produced in the vascular area, the deep layers of the skin, and hence may take several days to show much on the surface; meanwhile the collæmia which produced the asthma and also the skin troubles may have disappeared, so that the asthma may appear to alternate with the skin trouble, when it is really contemporaneous.

The relationship of asthma to nasal irritation and obstruction may be simply that these tend to diminish the free inrush of air in inspiration, and will thus tend to diminish for a time the atmospheric pressure in the chest, and so increase the congestion in the bronchial area; other things, as blood pressure, remaining the same.

It is interesting to note here that asthma is sometimes decidedly relieved by the use of compressed air ("Aerotherapeutics," Dr. C. T. Williams), which would from this point of view increase the inrush of air in inspiration, and also diminish the congestion in the bronchial area, thus increasing the space available for the incoming air.

Hay asthma, cat asthma, &c., may, in this way, be due to the irritant action of certain small particles in producing nasal congestion and obstruction with the concomitant action in the case of hay asthma, of heat, which increases the alkalinity of the blood and the amount of uric acid it will contain.

With regard to hay-fever there seem to be two chief factors, (1) the presence of vegetation with its irritating pollen, as in the case of hay; (2) heat or relative heat of a climate affecting probably uric acid and collæmia and the circulation; so that while natives of an elevated district may suffer, those who come there from lower and warmer districts obtain relative immunity from collæmia, and so find relief (see Solly, prev. ref., p. 156.)

Then again dust, even in ordinary asthma, will often account for the onset of an attack, as the dust of particular trades, fine particles of hay or straw, the dust of long railway journeys in dry weather, even the dust of unused rooms and old books; all these may act in much the same way, producing first of all nasal irritation and congestion, the bronchial trouble being secondary to the blocking of the upper respiratory passages thus brought about.

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Bad air and deficient oxygen may act by increasing the alkalinity of the blood, as I have pointed out that deficient oxidation probably produces collæmia in this way; hence the headache of badly ventilated theatres, and hot, crowded rooms (see pp. 46 and 83.)

Certain odours again may produce more or less nausea, which again will increase the alkalinity of the blood; and shock or fear may have much the same effect, and so precipitate an attack of asthma; and these last are well known to have a similar effect in chorea, which, as we shall see, is probably one more result of the effects of uric acid on the capillaries.

The drug, which of all others has been most widely used in asthma, is probably iodide of potassium, or the iodides; and it is interesting to find that they free the capillaries and lower blood pressure, which they are well known to do, by clearing the blood of uric acid (see fig. 21).

The iodides then probably relieve asthma by clearing the blood of uric acid and so reducing blood pressure and the resulting congestion in the area of the bronchial arteries; and I have given in my paper on "The Iodides,"[1] a figure to show the effect of Hair's asthma cure on the excretion of uric acid.

Of the action of acids, morphine and the nitrites I have already spoken, showing that they, like the iodides, clear the blood of uric acid.

Bleeding will obviously reduce blood pressure in the systemic circulation, and tobacco and lobelia are cardiac and muscular depressants, and probably lower blood pressure partly in this way (see also p. 265).

Antipyrin, I believe, acts as an acid, freeing the capillaries by clearing the blood of uric acid; but it may also act to some extent like the cardiac depressants just mentioned, and it seems probable that the fumes of sulphurous acid or of nitre paper may diminish the alkalinity of the blood, and so tend to clear it of uric acid.

And as I have before remarked, it is possible that the smoke of tobacco and other burning vegetable substances may contain similar acids, which act in the same way.

These facts leave in my mind no practical doubt that asthma is generally the result of the action of obstructed capillaries, and high blood pressure on the thoracic circulation, though as in the parallel case of the intracranial circulation certain local or general

[1] See *Medico-Chirurgical Transactions*, 1893, vol. lxxvi., p. 113.

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conditions may affect to an important extent the result produced in any given case.

I have also no doubt that the circulatory changes are generally due to uric acid in the blood (see "International Clinics," vol. iii., third series.)

If these deductions are correct the indications for treatment are moderately clear and distinct, and are only two in number, namely: (1) To reduce and keep down blood pressure; (2) to clear and keep clear the upper respiratory passages, so that the atmospheric pressure in the chest shall not be unduly reduced during inspiration.

Now blood pressure may be reduced either by freeing the capillaries or weakening the heart, and the iodides, morphine, calomel, or the salicylates free the capillaries by clearing the blood of uric acid, while acids, and probably the inhalation of acid fumes act in the same way.

Again, blood pressure may be kept down by reducing the amount of uric acid directly introduced or formed in the body, by altering the diet, and I have records of several cases of asthma where such alteration of diet has given great and permanent relief, and I have pointed out above that a diet containing an excess of animal food has been observed to do harm.

Blood pressure may also be kept down by stimulating metabolism when this is possible; for as metabolism goes up urea and acidity rise, and the blood is kept clear of uric acid (see chapter iv.) Now this may be done by regular graduated exercise, avoiding carefully the fatigue point, or by massage to improve the circulation and metabolism in the muscles and skin. Neither of these treatments, however, diminish the amount of uric acid in the body: on the contrary, they increase it, while they keep the blood clear, and when further stimulation of metabolism is no longer possible, as in old age, severe collæmia is sure to supervene, bringing ing all its troublesome consequences with it (see following chapter).

For this reason I consider that diet which permanently reduces the amount of urate in the body is better treatment than stimulation of metabolism, which, while it clears the blood, causes urate to be stored in the body, and this will give increased trouble at some future time. Iodides or other drugs which clear the blood of uric acid will produce the same result; but if they are followed by a course of salicylates the troublesome rebound may to some extent be avoided, though diet is, I believe, always the best treatment where it can be managed.

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The condition of the upper respiratory passages is generally a matter for the surgeon; but, as I think, there is reason to believe that an excess of uric acid in the blood may by affecting their circulation tend to produce or keep up congestion of the nasal and the other mucous membranes, I should be inclined, where such local troubles are slight and merely congestive, to give diet a careful trial before resorting to surgery.

Since the third edition of this book appeared, I have read a most interesting paper by T. H. Buckler, of Paris, in *The American Journal of Medical Sciences*, July to October, 1882, p. 347, a reference to which I owe to my friend, Surgeon-Captain Roberts, I.M.S.

It bears the title "Rheumatic leucoinitis of the pulmonary air tubes, and relating also to the pneumonia and solid engorgement supervening thereon."

I conclude that leucoinitis refers to the inflammation of the white fibrous tissues of the air tubes, which according to the author, are the chief seat of the disease.

He sees no reason to believe that the white fibrous tissues of the air tubes are any more exempt from disease than the fibrous tissues of other parts of the body.

The signs of this inflammation of the fibrous tissues of the air tubes (fibro-bronchitis) are: fever, cough which is dry, often paroxysmal, absence of signs of catarrh in the chest; such bronchitic signs may alternate with a rheumatic arthritis of the shoulder or other neighbouring joints, and the fibrous tissues of the endocardium, or pericardium may be affected in the course of the attack.

He calls this trouble rheumatism, but it is evident that what he really means is a gout of the fibrous tissues, and he refers to an article by Dr. Black, in the *Edinburgh Medical Journal* of 1854, who found crystalline particles of uric acid and urate of soda in the said white fibrous tissues.

After the air tubes have been affected in this way, the lung round or between them becomes pneumonic and solidified, and tends to remain persistently in that condition (rheumatic pneumonia).

Such pneumonia may change from place to place (metastasis) going from one bronchus to another, or from one lung to another, and affecting the heart on the way.

The great point about these rheumatic inflammations is that they yield at once to rheumatic treatment with salicylate of soda, but if the rheumatic element is not treated they are extremely intractable.

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Tubercle may find a nidus in the pneumonia so produced, and the phthisis which results may eventually leave no trace of the rheumatic inflammation in which it originated.

The cause of this rheumatic inflammation is generally exposure to cold or damp, or both, such as sleeping in wet clothing, etc.

The author considers that the salicylate acts by dissolving the uric acid out of the fibrous tissues; and it is most interesting to note that he believes that salicylates will not act well when the urine is alkaline, and thinks the best indication for their successful use is an acid urine turbid with urates, which clears on adding liq. ammoniæ. The other drugs he makes use of are phosphate of ammonium, which he regards as a very good solvent of uric acid, and fresh lemon juice, the latter to be given when there are phosphates in the urine.

He also considers that a London fog with low temperature may cause such rheumatic bronchitis and pneumonia, and these may produce very serious and fatal results if the rheumatism is not treated.

The cough is dry and paroxysmal, and if such a cough exists without a long uvula and with few or no chest signs, the disease is rheumatic fibro-bronchitis.

Curiously enough he also says that this rheumatic inflammation of white fibrous tissues is never attended by any pain, which is not only in marked contrast with the effects of gout in other fibrous tissues, but differs very much from my own experiences of gout of the trachea and bronchi, to be related further on, in reference to fig. 65.

Such is an outline of this most interesting paper.

My own experience leaves no doubt in my mind that uric acid causes inflammation of all these fibrous tissues, both of the digestive and respiratory tubes, of the pharynx and œsophagus on the one hand, and of the nose, larynx, trachea and bronchi on the other, and I have had most of them a good many times.

The trouble in the nose and pharynx causes burning and discomfort rather than pain; in the œsophagus there is pain with local tenderness, as of a bruise, as each bolus of food goes down. In the larynx there is a feeling as of a ring of dryness with a certain amount of burning, and as this passes down and involves the glottis there is hoarseness.

In the trachea there is similar dryness and burning, but if the inflammation is at all acute there is great burning pain as if the structures were red hot, and they feel as if badly bruised and most tender to cough.

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The whole of these troubles come as the result of exposure to cold, especially exposure after fatigue and perspiration; thus exposure to cold wind after getting one's beard cut a little too short will start a pharyngitis.

For some interesting points and facts as to the connection of diseases of the nose and throat with gout, rheumatism and asthma, and also for the record of a case where podagra and pharyngitis alternated, see the Lettsomian Lectures by Dr. de Havilland Hall, (*British Medical Journal*, 1897, vol. i., p. 449), and in my own case it will be seen in the description of fig. 65 that tracheo-bronchitis alternated with gout of the intestines.

I have been also much interested to hear from Dr. Mackie, of Nottingham, that he has noted an almost constant connection between catarrhal conditions of throat and ear, adenoids, &c., and the uric acid diathesis, and has read two papers on the subject before the Medical Society of Nottingham, and he says in a letter to me, "I scarcely see a case of adenoids, say in a child, but where there is an arthritic or migrainous parentage," and it is obvious that such conditions may quite easily result from recurrent uratic irritation. I may mention also that both my children had adenoids and enlargement of tonsils to a marked extent, and several families of cousins suffer markedly in the same way.

When at all acute, the inflammations of the nose, pharynx and respiratory passages end by the discharge of yellow pus, and no doubt the œsophagus does the same, being completely identical with what I shall have to describe in the next chapter as gout of the intestines, and this, as we shall see in my description of the circumstances and symptoms attending fig. 65, ends in the discharge of muco-pus from the bowel.

They are all, just as pointed out by Dr. Buckler, extremely amenable to treatment by salicylates, and their most severe symptoms subside within an hour or two after taking a dose of it; but as is also pointed out by Dr. Buckler, there is one condition which interferes with their action, namely, low acidity of the urine, which goes with high alkalinity of the blood, which as I have already explained, and shall again refer to in describing fig. 65, prevents salicylates from acting as solvents of uric acid, and so prevents their relieving these troubles.

Dr. Buckler's reference to the possibility of tubercle being engrafted on the top of such a gouty inflammation of fibrous tissues is most interesting; do we get here a possible explanation of the marked lowering of the temperature of phthisis by salicylate of soda which is well known?

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Is phthisis at certain stages an infective tubercular process plus a gouty inflammation of neighbouring fibrous tissues? I have considerable confidence that every so-called common cold originates somewhat in this way.

There is first an irritation of an exposed surface, as the nose or pharynx, by cold, dust, pollen, or other irritant particles, possibly by the microbes of catarrh themselves, and on this there supervenes, owing to the presence of plenty of uric acid in the blood, a gout of the neighbouring fibrous tissues, and then the gout and the catarrh microbes spread in all directions through these fibrous tissues, but the catarrh will not spread without the gout, hence salicylate of soda cuts short the process in a few hours, and those who have not excess of uric acid in their blood do not suffer from such catarrhal and gouty inflammations, hence the observed influence of milk diet, in preventing and relieving bronchitis (Semmola).

Does phthisis as Dr. Buckler partly suggests originate in the same way, the tubercle bacillus and the gouty "leucoinitis" working together and helping each other? if so we have a most interesting and possibly useful explanation of the connection between gout and phthisis, and this will also explain several points to which I have already referred in this chapter, such as the relation between phthisis and spring time, when there is in most people an excess of uric acid passing through the blood; its relation to dyspepsia and gastric troubles, which bring about a similar result, and its observed relation to pregnancy and parturition.

This also explains the late Sir A. Clark's experience, for though he, by feeding up cured his phthisis and got gout and collæmia later on, the first effect of his liberal diet, was as I have said with regard to the cure of gouty arthritis by a pure meat diet (chapter xv.) that he was stimulated by the diet and his blood was for a time kept clear of uric acid, and during this time, fortunately for him, the combined activities of gouty fibrosis and tuberculosis came to an end.

Do we not here also get further insight into the pathology of that disease in which the late Sir A. Clark himself took so great an interest, namely, fibroid phthisis? May this not be a condition in which the gouty fibrosis outruns the tubercle and eventually almost replaces it?

A bracing place or mountain climate again acts just as the stimulating diet above referred to, and keeps the blood clear of uric acid for the time, hence the microbe of catarrh can get no foothold,

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and the well known effect of such a climate in phthisis has most probably an identical chain of causation behind it.

But be this as it may, I can answer for it that a common cold can at once be cut short by one or two fractions of a grain of calomel (gr. $\frac{1}{4}$ to $\frac{1}{2}$ ter) followed by salicylate of soda (gr. xv. ter vel quater) for four or five days.

In my own troubles the only point is whether they are bad enough to require treatment, but there is never any doubt that I can cure them with salicylate if necessary; and the purpose of the above calomel is to partly clear the blood of uric acid and stimulate nutrition and thus produce a condition favourable for the best action of salicylates (see also remarks on fig. 65).

The whole of these gouty and catarrhal inflammations of fibrous tissues have one important characteristic, noted also by Dr. Buckler, namely, that they tend to fly from place to place, one getting better as the other gets worse; they also have another characteristic which they share with all other and better known gouty inflammations, and that is that when once a fibrous tissue has been affected the gout tends to return to it again and again when the least opportunity offers, or as I have elsewhere explained it, there is possibly left in these fibrous tissues a small residue of uric acid (such as that found by Dr. Black, quoted in Dr. Buckler's paper) which tends to attract more uric acid to come there at the first chance; and this shows us the very great importance of administering the salicylate for a sufficient length of time to clear out all the uric acid from the affected fibrous tissues, a principle which is somewhat blindly acted upon in the treatment of acute rheumatism, but not even then perhaps to a sufficient extent.

Before leaving this aspect of the causation of phthisis, I would call attention to the case of M. J., narrated in chapter xvi., where the administration of an acid and some strychnia produced an arthritis of a neighbouring joint, the shoulder (just as in Dr. Buckler's cases), and also probably an endocarditis of the mitral valve, and then salicylate of soda promptly relieved these troubles and brought down the temperature; I may say also that M. J. came of a decidedly gouty family.

It seems to me that we may gather some useful indications from the above pathology of phthisis, which, if well founded, may help us greatly in treatment.

With regard to catarrh, I am decidedly of opinion that those who live on a milk or uric acid free diet, are much less liable to it than meat eaters, and suffer less severely when they get it, and in old

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age also are, I believe, less liable to chronic bronchitis, so that I quite agree with the observation of the late Professor Semmola, that milk diet is good treatment for chronic bronchitis in the old.

In phthisis we may have to deal with two similar factors, a gouty inflammation kept going by an excess of uric acid in the blood, and a microbe which lives by its help. From this point of view I was much interested in a letter from their correspondent at Rome which appeared in the *Lancet*, 1897, vol. i., p. 214, and in which it was mentioned that certain pathologists in America and Italy were now much inclined to regard phthisis as a disease of nutrition rather than of infection, and I wrote a letter mentioning some of the above points which appeared in the same journal, p. 275.

And the obvious indication is to clear the blood of uric acid and to burn up the microbe; and this may be done as the late Sir A. Clark did it, by a stimulating diet which keeps the blood clear of uric acid for a time; but I believe there is a better way still, namely, first to stop the gouty inflammation, just as in catarrh, by a course of salicylate, and then to stimulate nutrition with a sufficiently nitrogenous, but entirely uric acid free diet, with tonics freely given.

We shall thus keep the body clear of uric acid as well as clearing it out at first, and when we burn up the microbe, we shall not create a store of uric acid which may return into the blood at some future time, and again come into partnership with the microbe, producing a relapse.

In this connection I have been much interested in the writings of Professor Mays, of Philadelphia, on the neurotic origin of pulmonary consumption and its treatment by strychnine,[1] for though I cannot agree with his pathology, I am not unmindful of the fact that migraine was called a neurosis, or nervous disease, till it was found to be due to poisoning by uric acid, and the neurotic element in phthisis may thus simply represent its relationship to gout. Be this as it may, the treatment suggested by Professor Mays seems to me to be one which is extremely likely to go to the root of the matter if slightly modified.

This treatment consists of administering large and increasing doses of strychnia, beginning with $\frac{1}{30}$ grain 4 times a day, and increasing week by week up to $\frac{1}{15}$, or even $\frac{1}{8}$ grain, 4 times a day, always, however, stopping short of the production of restlessness, twitchings,

[1] *New York Medical Journal*, Feb. 15, 1896, and *American Medico-Surgical Bulletin*, May 9, 1896, also article in *Journal of Nervous and Mental Diseases*, November, 1896.

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or other toxic symptoms. The rest of the treatment consists of feeding up the patient on a highly nitrogenous diet of egg albumen, and this part of it I have modified by substituting the albumen of milk, cheese and pulses, which introduce no uric acid or xanthin.

I have applied this treatment to several cases recently under my care generally after a course of salicylates, and as far as one can judge from a few cases with results which seem to promise well for the future, and one of these cases, where marked disease at the right apex with anorexia, high and irregular temperature, night sweats and wasting, slowly and steadily cleared up on the treatment, whether post or propter, I showed at a recent meeting of the Æsculapian Society, with the object of suggesting the use of similar treatment by others.

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CHAPTER X.

Dyspepsia and Gout of the Intestines.

As I have said, in the uric acid headache when the pain is severe, and mental and bodily exertion are almost impossible, when the skin and extremities are cold and the urine scanty, there seems to be good reason to believe that the circulation is equally defective in the glands and mucous membranes of the digestive system.

For the saliva is obviously scanty, and there are several well-known facts which render it extremely probable that gastro-intestinal digestion is almost completely at a standstill. The cases I have mentioned in chapter vii. must, I think, go a long way towards proving that this is so in some epileptic fits; and it must surely be common experience with those who see much of migraine and similar "bilious attacks" that in some of these conditions food may be vomited after several hours' sojourn in the stomach, in a totally undigested condition. I am suggesting that this is due to the defective circulation in the glands and mucous membranes concerned, produced by excess of uric acid in the blood, and that a bilious attack is a mixture of dyspepsia and collæmia, a vicious circle in which the one first on the scene produces the other; dyspepsia may be the first, and will produce collæmia; or collæmia may be the first, due to such a cause as fatigue for instance, and will produce dyspepsia.

Now it is clear that such defective circulation will account for the failure to digest and absorb either food or drugs, which characterises these conditions, and will further account for the putrefactive processes which, under these conditions, promptly take the place of digestion, they in their turn accounting for the changes in the urinary constituents noticed to take place in epilepsy by Drs. Herter and Smith (p. 216), possibly also for the somewhat similar evidences of intestinal putrefaction met with in some conditions of anæmia (see chapter xii.), and as we shall see also in chapter xii. they may very probably account for the causation of oxaluria and its frequent association with dyspepsia and hæmoglobinuria.

The extremely fœtid motions which are often met with in

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dyspepsia, bilious attacks, and diarrhœa are, I think, very often due to the cause of intestinal putrefaction just mentioned.

Then in chapter xii. I shall have to give notes of a case in which, along with these disturbances of the circulation in the stomach and intestines, there was very distinct evidence of congestion and enlargement of the liver, these being associated in some attacks with a temporary albuminuria.

I mention this to show the possible effects of these circulatory disturbances on the liver, and we can already demonstrate their effects on the kidneys; further to draw attention to the very close relationship in time between all these troubles, a relationship which I am endeavouring to show has its foundation in community of causation, and this very close relationship must be my excuse if in the chapters treating of these conditions I am driven to repeat to some extent what I have already said.

I must not forget, however, that my main point in this present chapter can be demonstrated by means of a very simple experiment. Let anyone swallow a few grains of salicylate of soda, and watch how long it takes for the reaction with perchloride of iron to appear in his urine. Under normal conditions he may very probably find it in from 7 to 10 minutes. Let him then repeat the experiment some other day, when his blood pressure is above normal, when he has a headache, a bilious attack, or other form of gastric upset, and when his pulse is slow and his urine scanty, he will find that the reaction in the urine does not appear for a considerable time, possibly, as in the case of epilepsy mentioned before, not for hours (see p. 217).

But failure of gastric digestion and absorption is not only a result of collæmia and the circulatory changes it produces, it is also a cause of further collæmia, for the failure of digestion and absorption diminishes the blood's income of tissue, foods and acid-forming substances, and this, added to the deficient circulation in all the great metabolic tissues, tends ever towards a more and more feeble metabolism with lessening formation of urea, and of acids and acid salts, and an ever increasing alkalinity of the blood and tissue fluids, which thus become ever better and better solvents of uric acid, and will take up more and more of it when it is available.

In this way, from collæmia to dyspepsia, and from dyspepsia to collæmia, we get a vicious circle which tends to extend itself and drag the patient down to ever lower and lower conditions of digestion and metabolism, and which must be completely broken through before any general improvement is possible.

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Such is, I think, the causation of a very large number of dyspeptic troubles, an originating disturbance as indigestible food, irregular food, food taken in sequence to fatigue and exhaustion (see chapter viii.), sudden changes of diet, or weather, exposure to cold causing depression, one or all of these causes, or more frequently a mixture of them, upsets gastric digestion, which in turn increases the collæmia, and the downward course begins, and if not promptly arrested, the patient becomes greatly reduced in strength and very anæmic (see chapter xii.), and then dyspeptic troubles become chronic, and for a time perhaps almost incurable. Then again, perhaps in the primary disturbance of gastric digestion putrefaction may supervene, and masses of food in this condition may act as irritants in the lower portions of the intestinal tract, and excite more or less local inflammation and diarrhœa.

In these conditions, as I have said, I believe that mercury and its salts act, not as local disinfectants within the intestinal mucous membranes, but by getting absorbed into the blood and clearing it of uric acid, with which they form insoluble compounds; digestion and absorption are thus once more allowed to proceed, because the capillary circulation throughout the intestines is restored, and putrefactive products soon cease to be formed.

All will, however, not be well in a moment; there may still be patches of gastro-intestinal irritation, due to the presence of the products of putrefaction and fermentation; and some diarrhœa may continue from this cause, and there will also remain some general lowering of nutrition and debility, and some anæmia, which will require special treatment in addition to keeping the blood clear of uric acid.

But supposing that before the process has been put a stop to some intestinal irritation has become considerable, passing in some places even into slight inflammation, it is clear that when by mercury or other drugs we clear uric acid out of the blood we may very probably get a concentration of this substance in the tissue fluids round about such foci of irritation, and this will be still more liable to occur if, as the result of disturbed digestion there has been fermentation with excessive formation of acids, rendering the intestinal mucous membranes more acid than usual.

Such a concentration of urates in the fibrous walls of inflamed areas of intestine, just as they concentrate round the lowly alkaline fibrous tissues in joints, and in the liver, spleen, and kidney, in several of which they may be present in quantities sufficient to be visible to the naked eye, constitutes what I have spoken of as gout

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of the intestines (*Practitioner*, vol. i., no. 1), and forms, I believe, the anatomical condition behind such troubles as colic, enteralgia, enteritis, and not a few cases of typhlitis.

And if there are present such foci of intestinal irritation, as the result of dyspepsia with putrefaction or fermentation of food substances, at the time when a dose of mercury drives uric acid out of the blood, it is little wonder that by still further concentrating the urates round the intestinal lesion it should greatly aggravate the trouble and produce severe gout of the intestines.

And we have also the evidence of Sir A. Garrod and others that urates may in this way produce severe inflammation of the intestinal walls, and may eventually be deposited there in such quantity as to form visible concretions.

Now Sir A. Garrod gives notes of the case of a very gouty man, aged 50, where, after exposure to cold, gout retroceded to the intestines, producing intense inflammation of the last eighteen inches of the ileum as found after death ("Gout and Rheumatic Gout," ed. iii., p. 439).

And Sir Dyce Duckworth says: "Professor Hayem has recorded a case where enteritis occurred, the villi being strewn with small uratic incrustations;" and further on he says: "Severe colic, tympanitic distension, enteralgia, and diarrhœa, are sometimes distinctly referable to gouty disorder" ("A Treatise on Gout," p. 89).

From these remarks it might very reasonably be supposed, that though the conditions mentioned do occasionally occur as the results of gout, they are somewhat rare, and therefore of little clinical importance.

My clinical and experimental experience has, however, led me to take a very different view, and to believe that a very large number of cases, such as I have mentioned, are neither more nor less than a gout of the walls of the intestinal tube, and that a knowledge of their true pathology places us at once in a position to effect a complete and satisfactory cure, by the use of the same drug, which in my hands gives the best results in cases of arthritis, due to uric acid.

I shall further point out that such colic or enteritis can be produced by giving certain drugs, all of which have the same action on uric acid, viz., that of driving it out of the blood into the tissues.

Prominent among these drugs are the metals, mercury, lead, and zinc, all of them forming, as I have pointed out, insoluble compounds with uric acid, and I believe also that lead colic can

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be successfully treated by the same drug that is useful in gouty arthritis, and that lead colic is simply an enteralgia or enteritis, produced by the irritant effects of urate of lead in the intestinal walls.

I shall now have to point out that the same result can be produced by urate of mercury, urate of zinc, or even by urate of soda.

As in several other matters connected with gout, it was my own personal experience that first directed my attention to the points I am now bringing forward.

Some eight or nine years ago, I noticed that when I was suffering from some gastro-intestinal trouble, such as that which commonly produces an attack of uric acid headache (migraine), and that when I treated this trouble by taking a small dose of calomel, I sometimes produced pretty severe intestinal pain, which was generally located in or about the right iliac fossa.

On one occasion, when a small dose of calomel (gr. i.) produced slight pain in this way, I thought that the purgative action had been insufficient and that a larger dose was indicated; the result of this, however, was to produce very severe pain indeed, which confined me to bed and the house for several days, and made me quite unhappy about myself, as I feared that I had typhlitis.

At this time, however, I knew very little about gout of the intestines, and nothing at all about the solubilities of the urates of mercury, hence beyond a mental note to avoid, as far as possible, the use of calomel for the future, the lesson was lost upon me.

A year or two later, when taking some cocaine for purposes of experiment, I was surprised to find that it was followed on several occasions by a somewhat similar pain; and this pain, partly due I think to cocaine, and partly the result of cold and occasionally wet feet late in the autumn, became chronic with relapses, and awakened my old fear of typhlitis and of serious disease.

So much was this the case, that I consulted a friend on the matter, and, at his suggestion, was making up my mind to take several months' rest and change of climate, when I chanced (still following out my experiments to some extent, or possibly prompted by some previous experiences) to take a few doses of salicylate of soda; and the effect was magical; the pain was better soon after the first dose, and in two days was gone for good and all.

I now began to see that I was not suffering from serious organic disease, but from a gout of the cæcum, accompanied by a certain

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amount of colic enteralgia and enteritis, and when I afterwards found out the insolubility of the urates of mercury, I was easily able to understand why this metal had produced the pain on a previous occasion and why salicylate of soda had cured it so completely on this last occasion.

Since this time I have had no further anxiety on the score of this intestinal disorder; I have often had it, and will undertake to produce it at any time, by the use of any of the drugs I shall mention presently; but I have now complete confidence that I can put an end to it in a few hours' time by means of salicylate of soda.

One of the first uses I made of the knowledge I had thus acquired, was to apply the same argument to lead colic; here is another metal whose urate is insoluble (Garrod). I have shown that, like mercury, it diminishes the excretion of uric acid and clears it out of the blood, and like mercury, it produces intestinal irritation and colic; if this is so, salicylate of soda ought to be useful in lead colic.

And in the cases in which I have been able to give it this has certainly appeared to be so, and all symptoms cleared up steadily and completely, the patients doing fully as well as under any other treatment with which I am acquainted. Similar cases of colic, in which, however, there is no sign of the presence of lead to be made out, will often yield to salicylate of soda more quickly than to anything else; and I have also treated several cases that were clinically typhlitis in the same way, and have every reason to be satisfied with the results.

One of these was in the person of a relative of my own who is a member of the profession. I happened to hear that he was ill with what sounded like typhlitis, and I also heard that he had taken a dose of calomel shortly before the attack began. It at once struck me that this was a repetition of my own experiences, and I went to see him as soon as I could, told him what I had found out in my own case, and persuaded him to let me add a little salicylate of soda to the mixture he was taking.

The result was in every way as satisfactory as in my own case; he at once began to improve, and in two or three days was up and about, while prior to the administration of this drug it appeared only too probable that his illness would be a matter of weeks.

The history of this case is as follows. After one or two rather extensive dinners and champagne, he had a little digestive dis-

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turbance, and with the intention of putting this right he took a few grains of calomel, and a few hours later was seized with violent, colicky pain in the right iliac region. The pain came in attacks which were worse at night and caused nausea. There was an ill-defined fulness, with tenderness in the right iliac fossa, and temperature about 100°F. He asked a neighbour to come and see him, and lay in bed often groaning with pain, and with warm poultices constantly applied to the painful region; he took a mixture containing nepenthe and carminatives, and a nurse was obtained for him.

This was the condition of things when I went to see him, and with the concurrence of the neighbour who was looking after him, added salicylate of soda to the mixture, with the result mentioned.

There was, I think, no doubt in the minds of any of us that we were dealing with typhlitis, or a condition so like it that it deserved to be treated with great respect; but there was also in my mind no doubt from the history of its causation that it would yield at once to salicylate of soda, and this proved to be the case.

Among drugs with which I have from time to time produced somewhat similar intestinal troubles in myself are, in addition to lead and mercury, zinc which I have taken as the sulphate and as the phosphide, and Dr. Ringer mentions zinc colic ("Therapeutics," ed. xii., page 254); and copper, of which the same author says (p. 252): "Copper salts taken for a considerable time in small quantities are said to give rise to a condition not unlike that produced by lead; for example, colic with alternating constipation and diarrhœa, and it is even said paralysis of the upper extremities, undistinguishable from that of lead." (See also a note on the effect of peas coloured with copper, in the *Lancet*, 1892, vol. i., p. 1445.)

I have, myself, had a patient under my care who worked in brass, and had troubles resembling uric acid headache, which she attributed to her work; and what is described as brass-worker's ague has many points of resemblance to a severe attack of migraine. In these cases uric acid headache was no doubt due to an overflow of uric acid into the blood from that which had previously been locked up and retained in insoluble combination with copper. And we know that urate of copper is insoluble, as a process for estimating uric acid is founded on the fact. (Arthaud and Butte, *British Medical Journal*, 1890, vol. i., p. 495.) The parallel, therefore, with lead and mercury is complete.

In addition I have mentioned the pain produced by cocaine, and

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cocaine also diminishes the excretion of uric acid, and acids, nux vomica and sulphates, especially sulphate of soda, occasionally act in the same way and cause some intestinal pain of a similar kind; and exposure to cold, or cold feet in winter, occasionally produce the same result, and all these factors have the same action on uric acid; they diminish its excretion in the urine, clear it out of the blood and drive it into the liver, spleen and fibrous tissues, especially into any fibrous tissues that have had their alkalinity diminished by any previous irritation or inflammation. They produce this effect on uric acid either by forming insoluble compounds with it, as in the case of the metals, or they diminish the solvent powers of the blood by diminishing its alkalinity, and under slightly different conditions any of them may produce gout of a joint, instead of gout of the intestines.

No one, I suppose, will deny that there is a large amount of fibrous tissue in the walls of the intestines, and if the fibrous tissues in fascia, tendons, and joints, and as we have seen also in the previous chapter those in the respiratory and upper digestive passages are liable to have urates deposited on them when they have had their alkalinity diminished by cold, injury or irritation, I see no reason why the fibrous walls of the intestines should not be affected in exactly the same way.

Thus the case just quoted from Sir A. Garrod's book might have a causation somewhat as follows:

A gouty man has more or less acute intestinal irritation (of dyspeptic origin) causing some nausea; this produces collæmia; on this there unfortunately follows exposure to cold, which raises the acidity and drives the urate out of the blood again, and, as in other cases a large amount of it goes into that piece of fibrous tissue which is most irritated and least alkaline—in this case the fibrous structure in the walls of the last eighteen inches of the ileum—this still further increases the irritation and acute gouty inflammation of this portion of intestine ensues, and becomes so serious as to cause death.

I have no doubt that if after death an extract had been made of this portion of the ileum it would have been found to contain far more urate than any other portion of the intestines of the same weight, and we see from the points mentioned by Sir Dyce Duckworth (previous quotation) that the gout may go on to deposit of urate visible to the eye.

I have recently had an opportunity of testing a piece of inflamed intestine for uric acid in the case of Alice C., aged 12, admitted

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under my care at the Royal Hospital for Children and Women on November 11, 1895.

She had been suffering from appendicitis or perityphilitis for some three weeks, and this had probably gone on to local suppuration before she was seen.

She was put on salicylate of soda, which was given by rectum when she vomited after it, but this did not produce any marked effect, and she died on the fifth day after admission with general peritonitis.

I am in doubt in this case whether she got enough salicylate owing to the vomiting which was present on admission; or whether the salicylate failed because suppuration had already taken place, as in my experience it is quite useless in gouty arthritis once suppuration has set in.

At the *post-mortem* a local abscess round the appendix was found, which had burst into the general peritoneal cavity shortly before death.

I then took a portion of the cæcum with the appendix at the seat of the local abscess, and also a portion of the colon from the opposite side of the abdomen near the splenic flexure, and tested them for uric acid in the ordinary way.

I found in the portion of cæcum and appendix ·053 gr. to oz. of uric acid or xanthin, but in the splenic flexure so little that I could not feel certain that there was any at all; while in the extract of cæcum the precipitate with nitrate of silver was quite visible.

I think it probable that the pus of the local abscess would have contained more uric acid had we been able to get it; and that the inflamed intestine would have contained more earlier in the disease.

I should lay absolutely no weight on my results in this single case, but record it here merely with the object of getting others to repeat my observation whenever they have a chance, either in perityphlitis or the colic produced by lead or other metals.

Again we have some evidence pointing in the same direction in the part of the intestine commonly affected; why should the last eighteen inches of the ileum, or, in my experience, the cæcum and lower ileum be the parts affected?

I would suggest that the reaction of the intestinal contents has something to do with it; it is well known that those of the large intestine have an acid reaction, and it is not improbable that the alkalinity is diminished in the small intestines before the ileo-cæcal valves are reached.

Again, M. Bouchard ("Lecons sur les Auto-intoxications," p.

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172), has shown that in certain dyspeptic conditions, especially in dilatation of the stomach, there is an excess of acid throughout the whole intestinal canal, and such acidity may cause local irritation, and thus form the starting point for a concentration of urates in the intestinal walls and an attack of gout.

Then any local irritation due to impacted fæces or foreign bodies may act in the same way, setting up a local inflammation with fall of alkalinity, which is soon complicated by a concentration of urates on the irritated spot; in this way irritation in the vermiform appendix may precipitate a local attack of gout, which, as in other parts, the joints and valves of the heart for instance, recurs and recurs till a more or less extensive lesion (perityphlitis) has been produced.

I notice that recent writers on this subject generally make use of the term appendicitis, and if proof is forthcoming that the trouble originates in the appendix there is no objection to this. As regards its gouty or rheumatic origin, it makes no difference whether it begins in the appendix, the cæcum, or the lower ileum, as in the case recorded by Sir A. Garrod; the only thing that concerns us is that these portions of intestine contain fibrous tissues upon which urates may be precipitated if their alkalinity is diminished by such things as dyspepsia, cold or irritating substances. And the irritation so caused may recur and recur and lead on to ulceration and sloughing, just as in any other fibrous tissues.

But it will be said if the reaction of the intestinal contents has anything to do with the gout attack and its localisation, then surely the stomach should be the place of all others in which these gout attacks should occur.

We all know the way in which the stomach is prevented from digesting itself by the free circulation of alkaline blood in its walls, but let there be local irritation, inflammation or stasis, then the acidity of the contents does affect the structure of its walls, and it does proceed to digest itself to a certain extent, and I can quite believe that such a local irritation may be kept up and made to recur by urate irritation; and Sir Dyce Duckworth mentions the conditions found in one or two cases of gout of the stomach (prev. ref., p. 89). And I have seen several cases of what I suppose would be called gastralgia, where the pain has yielded in the most prompt and decided manner to salicylate of soda. In one such case the trouble had continued for more than twenty-five years, it came in attacks lasting seven to ten days, which were worst in winter or on exposure to cold, and better in warm rooms; the

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attacks were also made worse by calomel, aperient waters, or acids, and there was a family history of gout; the pain was in the epigastrium, and was described as being like toothache in the stomach. It is not a little remarkable also in how many cases of gastric dyspepsia one finds salicylates useful in relieving the pain.

I would suggest that those who in future are able to estimate the amount of lead in the organs and tissues of fatal cases of plumbism, should estimate at the same time the uric acid, to see whether they are present in their combining proportions, and therefore probably as urate of lead.

Professor Oliver in his interesting work on "Lead Poisoning" (p. 38) points out that during an attack of lead colic the pulse becomes hard, resistant and slow, and the urine becomes scanty and of high specific gravity; the action of urate of lead will explain every fact here mentioned.

While the lead is causing retention of uric acid (its first action) the pulse is quick and soft, the capillaries are free, and the urinary water is profuse; but later on, urate of lead which carries uric acid out of the blood, and so frees the capillaries, is deposited in various organs and tissues, among others in the walls of the intestines; here it gives rise to pain and colic, and this quickly changes the whole condition, giving rise to the rebound or second action of lead.

The intestinal pain and colic produce nausea and failure of digestion and absorption. As a result of this, the acidity of the urine quickly falls, and the alkalinity of the blood rises, this dissolves out some of the urate stores and floods the blood with uric acid, which in turn causes the obstructed capillaries, slow high tension pulse, and scanty urine.

Precisely the same series of events can be brought about by any drug or combination of drugs which have the same effect that lead has on the solubility of uric acid, and what I have called the rebound after mercury, opium, zinc, cocaine, or acids, and nux vomica reproduces all the phenomena that attend lead colic, as described by Professor Oliver.

But it will be said if the rising alkalinity dissolves out the urate of lead it ought to remove that which is irritating the walls of the intestine and put an end to the colic; and so it eventually does, and this is nature's mode of cure; but inasmuch as there is a considerable amount of local irritation and inflammation in the intestinal walls, the alkalinity of the fibrous tissues is lower here than anywhere else in the body, and this is the last place the rising

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alkalinity affects, and meanwhile the pain and the inflammation go on.

But if at this time salicylate of soda is given, it acts as I have shown best in conditions of low alkalinity, and it dissolves out, and removes first of all the urates in the irritated intestine, because that is the place where the alkalinity is lowest; hence, as observed, it very quickly and completely relieves the colic, and it does this equally well whether it has to deal with urate of lead, urate of mercury, or urate of soda, and for the same reason that it is so useful in gout and rheumatism, because, as I have pointed out, it is a solvent of uric acid (*Med. Chir. Trans.*, vol. lxxi.)

But urates may undoubtedly affect other structures that contain fibrous tissues, and, as mentioned at length in the previous chapter, I have seen them so affecting the pharynx, larynx, trachea and large bronchi on the one hand, or the œsophagus on the other, and such inflammations are often brought on by exposure to cold in exactly the same way as the other gouty inflammations of fibrous tissues we have been speaking of. When gout affects the œsophagus, it causes severe pain just at one spot behind the sternum, and every mouthful of food swallowed seems to pass at one point over an extremely tender bruised surface; fortunately a single dose of salicylate almost completely removes it, but I believe that when not so treated it may sometimes spread to neighbouring fibrous tissues, as the pericardium or the diaphragm, and produce more serious results.

Further there is this point of great interest with regard to such uratic inflammations of fibrous tissues, that while they are commonly produced by the local effects of cold, when there are salicylates in the circulation, cold has absolutely no power of producing them, on the contrary warmth or the administration of alkalies will now make them worse, and cold or administration of acids better (see the record of my own experiences with reference to fig. 65, and the record of similar facts in others in chapter xvi.). And so far as I know there is no possible explanation of these facts except the well known differences in the solubility of uric and salicyluric acids respectively.

Uric acid is soluble in alkalies and insoluble in acids, hence it is precipitated by cold, which diminishes locally the alkalinity of the blood and tissue fluids.

Salicyluric acid on the other hand is soluble in slightly acid fluids, insoluble in alkaline ones; hence cold aids its solution and warmth hinders it; hence as recorded by many observers, warm

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clothing or warm weather makes gout or rheumatism worse under salicylates, while keeping the affected parts cool makes them better, and it would be interesting to know how often salicylates have been blamed for not curing gout or rheumatism through ignorance of this fact, and consequent neglect to keep the parts cool. As I shall point out in chapter xvi. salicylates act very badly in the warm climate of India, and some practitioners refuse to call the arthritis there met with rheumatism, because salicylates thus fail to relieve it; but if they could keep their patients cool, this difficulty about names would disappear.

For exactly the same reason salicylates do not act well, as noted by Dr. Buckler in the paper quoted in the previous chapter, when the urine is neutral or alkaline, but he did not know the reason of this, and therefore did not know that he could make them act well by giving acids in alternate doses with them, or keeping his patients cool.

These inflammations again can be cured by either alkalies or salicylates separately; but they cannot be cured and are made worse by a combination of the two, and for those who still regard rheumatism as a disease of microbic origin, this fact remains, I believe, absolutely inexplicable.

Then again I have long thought that it is at least possible that looking to the way in which carcinoma tends to attack seats of local irritation, it may often have its way paved for it by the chronic and recurrent local irritation produced by urates in the tissues.

And this has been further suggested to me from time to time by the interesting articles on the subject published by Mr. D'Arcy Power (*British Medical Journal*, 1893, vol. ii., p. 830, and the same journal, 1895, vol. i., p. 910), and others (see *Lancet*, 1893, vol. i., p. 1443).

Then cancer has been said to be rare among vegetarians (*British Medical Journal*, 1888, vol. ii., p. 29, and *Lancet*, 1888, vol. ii., p. 552), and Dr. Berkhart has pointed out the resemblance between the structure of a gouty tophus and a sarcoma (*Lancet*, 1893, vol. ii., p. 1500).

I think these points are worth bearing in mind, though at present they do not prove much.

In this connection a case recorded by Dr. Gowers in the *British Medical Journal* (1894, vol. ii., p. 1222), in which a patient who suffered from gastric troubles was treated by oxide of silver for a long time with the result that he got argyria with wrist drop, became very gouty, and eventually died of cancer, seems of some

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interest. Dr. Gowers considered that there was no connection between his other troubles and the new growth; but if there is anything in the above suggestions, then surely this man's tissues were subjected to very widespread irritation by urate of silver.

But my experience with regard to gout of the stomach and intestines has been shared by others, as I notice in Dr. Goodhart's work on "Diseases of Children," ed. ii., p. 545, a frequent stomach-ache is described as a "feature of the rheumatic child," and he also mentions that Dr. Marshall uses salicylate of lithia for this complaint, "he thinks with great advantage."

Speaking of stomach-ache reminds me that I have also myself seen several cases in which persons who had indulged in some excess of acid drinks in the summer, got as a result a more or less severe stomach-ache, and possibly some of these cases also are really gouty enteralgias, the acid acting in the same way as the drugs mentioned.

And again, Dr. G. A. Sutherland, writing "On some Symptoms associated with the Uric Acid Diathesis in Children" (*Brit. Med. Jour.*, 1892, vol. i., p. 856), mentions two cases of inflammation of the vermiform appendix, with marked tendency to recur, and even suggests that the calculi found in the vermiform appendix are composed of uric acid or oxalic acid.

I am indebted for the notes of the following interesting case to Dr. G. D. Logan, of Ecclefechan, the treatment, which he adopted with success, having been suggested by my writings on this subject.

"Called at 2 a.m., on March 15, 1893, to a case in the country, and asked to bring morphine with me. Found a woman, unmarried, about 24 years of age, suffering from severe abdominal pain and retching. Had arrived the previous day from Glasgow, where she had been for some weeks previously, more or less confined to bed with similar symptoms.

"Illness began in January, 1892, with a severe attack of diarrhœa which 'gradually turned into dysentry,' and though under constant treatment, she had never quite recovered from the looseness of the bowels and pain. In October of the same year she broke down completely, was sent to bed, and had a course of blisters and iodine on the abdomen, with morphine injections. As this gave no improvement she saw a consultant, who said that her womb and appendages were normal, that she was suffering from some neurosis, and advised a course of massage. This she had for a month; says she felt worse for it, and latterly could not bear the pain of rubbing.

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"For the last three weeks the pain had been getting more severe, and she had vomited almost everything taken. She now requires two injections of morphia daily (gr. ½ each), and can get no rest or sleep without them. She had for years been subject to severe, often 'recurring nervous headaches.' She had on one occasion been confined to bed for six months, as the result of a fall injuring her spine, but without any obvious lesions. She is not hysterical.

"On examination I could find nothing abnormal but the tenderness on pressure all over the lower part of the abdomen, her hands were very shaky, and she was much run down in strength.

"I thought it would be a good test case for the treatment you advise, especially with the morphine habit she had developed. I stopped the morphine at once. I ordered fomentations with belladonna for the abdomen. Soup and milk for diet, and a mixture with soda salicylate, nux vomica and gentian.

"After the second night she was able to get sleep, though she missed the morphine greatly, but at the end of a week she did not miss it at all. She got six or seven hours' refreshing sleep every night, and the pain was much less.

"In ten days she was out of bed, and in three weeks she was able to go out walking. Had an excellent appetite, pain all gone, bowels quite regular, sleeping perfectly, and since then she has remained quite well."

This is an extremely interesting case, for it illustrates so completely many of the points I have mentioned.

First of all the "nervous headaches" which I should have very little doubt were due to uric acid, then the diarrhœa which became chronic, doubtless with considerable local irritation in the intestines. On the patches of local irritation urates were from time to time concentrated, and the treatment by morphine, which for a time cleared the blood of urates would favour their action in keeping up the intestinal irritation, hence she got steadily worse on the treatment; but as soon as a drug was given which removed uric acid from the body, in place of causing its storage in the tissues, the whole thing cleared up.

I must congratulate Dr. Logan on the thoughtful care which led him to apply my reasoning and suggestions to this case, and on the great success he obtained when others had failed.

Since I first wrote on this subject, I have seen and heard of quite a number of more or less similar intestinal or abdominal pains, which were promptly relieved by the administration of salicylates.

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Thus Dr. Charles E. Lockwood, of New York, writing in 1894, mentions the case of a lady who suffered from pain and soreness in the neighbourhood of the cæcum, and had also one of her finger joints enlarged, and he reported that the pain and soreness began to leave her after the first dose of salicylate.

Dr. John Watson, of Newbury, Berks, writing in the same year, reports the case of an old gentleman suffering from very severe gouty gastritis; potash and soda with bismuth were given for a week or two with very little success, and then coming on my article in the *Practitioner* (prev. ref.), he was induced to try salicylate of soda; "the effect was simply magical, he lost all pain after taking the first dose, and has had none since; his dyspeptic symptoms have almost entirely vanished now after four days' treatment, and the drug has acted like a charm."

Dr. B. Yeo has written about rheumatic perityphlitis in the *British Medical Journal*, 1894, vol. i., p. 1189, and the author called attention to his previous writings in a letter to the same Journal, p. 1413. Interesting cases of appendicitis cured by salicylates, are recorded by Dr. Brazil in the *British Medical Journal*, 1895, vol. i., p. 1142, and Mr. J. E. Frazer, in a letter in the same journal, p. 1320, points out that morphine may do harm, a fact which is also noticed by Dr. Yeo, and is, I think, in evidence in Dr. Logan's interesting case, and I see also in the *Lancet*, 1896, vol. i., p. 640, the record of a case of rheumatism of the orbital cellular tissues, followed later by perityphlitis, both troubles yielding to the administration of salicylates.

Diagnosis of the dyspepsia, which is due to collæmia, depends rather on the symptoms which accompany it, than on its own special characters, and where dyspepsia occurs in relation with high blood pressure, headache, fits, or mental depression, asthma, Raynaud's disease, paroxysmal hæmoglobinuria, or Bright's disease, or alternates with gout or rheumatism, as in the case mentioned in chapter viii., there is a strong presumption that collæmia is at least one of the factors in its causation and continuance. Then it will improve on drugs or diet that clear the blood of uric acid, and will be made worse by administration of urates (see figs. 24 to 28).

In the same way gout of the intestines is to be diagnosed from its relation to the taking of metals and drugs which, under other circumstances, might cause gout of a joint, as mercury, or lead; or the effects of acids, acid salts, cold, &c., as in the cases mentioned.

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The indication for treatment in the case of the dyspepsia is to keep the blood free from an excess of uric acid. In the case of gout of the intestine, it is to remove the urate from the irritated part as quickly as possible, by means of salicylate of soda.

But in both conditions salicylates are extremely useful, and I now often find myself adding them on to bismuth in conditions where I should previously have given the latter alone.

The treatment of a bilious attack is the same as that of migraine, first clear the blood of uric acid, and then give a course of salicylates to carry it out of the body.

Gout may also affect other fibrous tissues almost within touch of the cæcum, such as those which surround and support the pelvic organs of the female, and where inflammation of such tissues occurs in a patient who has other evidences of gout or rheumatism, or only a family history of these, salicylate of soda should not be neglected, and what has already been said in this and the previous chapter about gout of other similar fibrous tissues should be kept in mind.

The treatment of intestinal putrefaction is much the same as that of the migraine or epilepsy which it accompanies, and those who are specially interested in this matter, will find an abstract by the author in *Brain*, September, 1895, on intestinal putrefaction in certain neuroses.

It is a fact of no little interest that salicylate of soda which cures all these intestinal pains and colics will under certain conditions, not only fail to cure them, but will even produce them when not otherwise present. And these conditions are exactly the same as those in which it also fails to cure rheumatism, or may even, as we shall see in chapter xvi. and fig. 62, make the pains worse and raise the temperature.

Now salicylates act best in colic, just as in rheumatism, when the trouble is acute and accompanied by fever; they also act best in the evening and early hours of the night, and least well in the morning hours, and in these morning hours people who are taking salicylates for quite different troubles may complain of some very decided colicky pains.

And these colicky pains while taking salicylates have these further interesting characteristics that they are worse while warm in bed, and are made better by getting up and having a cold bath (see also description of fig. 65).

But we have seen that the colic produced by urates alone without salicylates is made worse by cold and improved by heat, and the pains of rheumatism are, apart from salicylates, made better by

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heat and worse by cold; but under salicylates they are made better by cold and worse by heat, as we shall see in chapter xvi.

We shall there also see that external warmth acts like a dose of alkali, and increases the alkalinity of the blood, and also that salicylates act best when the alkalinity of the blood is low, and may not act at all, or even do harm when it is high.

And the fact that such colic is made better by warmth apart from salicylates, and worse by warmth conjoined with salicylates, shows that it is absolutely dependent upon the solubility of uric acid in the blood, and is made worse by anything which interferes with that solubility, and better by anything which aids it.

Now, apart from salicylates, external warmth raises the alkalinity of the blood and increases the solubility of uric acid, it therefore does good in colic; but when salicylates are in circulation, warmth, which raises the alkalinity of the blood hinders the solvent action of these substances for uric acid, and therefore makes the colic worse.

I will not go into this matter further here, except to point out its bearing on treatment, but must refer to what I have already said in chapter ii. on fig. 8 and shall have to say in chapter xvi.

Now it is obvious that if salicylates are not good solvents of uric acid when the alkalinity of the blood is high, they may fail to relieve colic such as that produced by lead, when it has lasted some time, and has consequently greatly lowered urea and acidity of urine, and raised to a corresponding extent the alkalinity of the blood, and that in such conditions their action will be aided by giving them with ammonia, which raises the acidity of the urine, or in alternate doses with acids or salts, which raise the acidity.

It follows also that when we are trying to cure colic with salicylates, and have got the patients well under their influence we must not go on with the application of hot poultices or fomentations to the seat of pain.

Much more also does it follow that we must never expect the best action of salicylates in colic, or for that matter, in rheumatism either, if we persist in giving them along with the alkaline salts of potash or soda, and indeed the satisfactory action of salicylates in acute rheumatism and their very doubtful benefit in the chronic disease is probably entirely due to the different reaction of the blood in these two conditions.

In the dyspepsia and slight colicky pains produced by urates or by urates and salicylates together, there is generally a little rise of temperature, say to 99° or 100°, and I have several times noticed in

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children who are taking salicylates for a cold perhaps, that the temperature is often raised to this extent in the early morning hours, but falls to normal when the drug is left off; no doubt in these cases salicylates and alkalies are causing in the morning hours when their actions clash, some little gouty irritation somewhere which suffices to raise the temperature to this extent.

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CHAPTER XI.

Raynaud's Disease.

Just as we have seen in the previous chapter, that the defective circulation in the gastro-intestinal mucous membranes produced by uric acid, may account for many of the phenomena of dyspepsia, I think that there is good reason to believe that the defective circulation in the skin and extremities similarly produced, will account for the production of Raynaud's disease.

The defective circulation is indeed common to the whole body, but the skin and extremities are specially affected, because, as, Raynaud points out, they are the parts of the body which are most exposed to loss of temperature, and because as we have seen in chapter v. cold is itself a powerful contributing factor in the causation of collæmia, and the extremities again have a larger surface, in proportion to bulk, than any other part of the body.

It may be said then that Raynaud in his "Thesis," published in 1862, attributed the local asphyxia and symmetrical gangrene of the extremities which he described to a spasmodic contraction of capillary vessels.

He acknowledged that this might be a general condition, affecting the vessels all over the body at the same time, but producing serious effects only in the extremities, because these are the portions of the body which have most surface in proportion to bulk, and therefore most quickly lose their heat by conduction and radiation, and most early become cooled down below the point at which the life of the tissues can be continued ("Thesis," p. 166). He observed that at the time of an attack of asphyxia or gangrene of the extremities, the skin was everywhere cold and pale, and a case of which I shall presently give notes shows, I think, that the temperature of the body at a distance from the seat of attack falls at the time of an attack, and rises again as it passes off; bear in mind also fig. 5.

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I shall also point out that there is good reason to believe that the vessels of the kidney are obstructed at the same time with those of the skin, and Raynaud himself mentions the signs of this without understanding their import; and there is also as we have seen some reason to believe that the vessels in the brain, lungs, and other viscera are in a similar condition.

Raynaud himself, however, gives no good or satisfactory reason why the arterioles and capillaries should be affected by this spasmodic contraction: it is true, he remarks, that it is often met with in nervous people, and those who suffer from hysteria, epilepsy, &c.; but what influence he attributes to the nervous system in producing these phenomena all over the body is not very clear.

At this point I think that my researches come in, and I have suggested that the vessels are contracted or obstructed owing to the presence of uric acid in the circulation (*British Medical Journal*, February, 1889, p. 191).

I will now give notes of some cases, and will then discuss Raynaud's cases and argument.

Margaret C., aged 3 years, came among my out-patients September 23, 1889. Her mother said that some of the toes of both feet were cold and blue, and the child complained of pain in them. The right foot was seen to be blue-black, cold, and tender, as far as the middle of the metatarsal bones, the left foot had the second, third, and fourth toes blue-black and cold, and the colour extended in lines a little into the sole of the foot. Second sound of heart relatively loud. Pulse irregular and marked plus tension. Had measles twelve months ago, and pertussis the same time. Has not had any fever lately. Has three sisters who are all well.

Father subject to gout, his family also subject to it and to phthisis. Mother well.

The feet were wrapped in wool and a quarter of a tabella of nitroglycerine given frequently, and she was admitted.

Sept. 24.—Much better. Feet are hot and a little tender, but the colour and coldness have both gone. Pulse 120; heart, first sound rather weak, second sound relatively loud. Urine of the attack yesterday gives a uric acid urea relation 1 to 8·3. An enormous excess of uric acid, but there is no albuminuria. Given a little dilute nitro-hydrochloric acid and ♏i. of tinct. opii. twice a day.

September 26.—Going on well; urine of this day gives a relation, of uric acid to urea 1—20·7.

September 27.—Had another attack in the evening, the left foot

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being most affected this time; it was blue as far as the ankle. In the right foot only two or three toes were blue, just the reverse of the previous attack. Was again given nitro-glycerine. Urine of the attack (probably a mixture) gave uric acid urea relation 1 to 22. Urine later on, after all the nitro-glycerine had been given, 1 to 53. The first lot of urine was a considerable quantity, 450 cc., and probably included urine before as well as during the attack; hence the relatively small amount of uric acid—1 to 22—as compared to 1 to 8 in first attack. The great effect of nitro-glycerine on the excretion is well shown in the excretion 1 to 53, which is in marked contrast with 1 to 22.

September 28.—Nearly all right again and only a few scattered petechiæ and some œdema marked the parts of the feet affected yesterday.

It was now noticed that there was some peeling on the hands and chest, and, thinking that she might have had scarlet fever, she was sent out.

Her mother denied that she had had any rash or sore throat previous to admission, and I saw her a few days later at her own home, and examined her sister, who showed no signs of peeling.

Eliza H., aged 6. Admitted under my care in the Royal Hospital for Children and Women, November 27, 1890.

Her family have always lived in London. There are three brothers and sisters younger, and one older than the patient. Mother has had nine children born alive, no miscarriages.

Mother is subject to cough.

Mother's mother and mother's brother had rheumatic fever.

Father's mother had "chalk gout."

No ague in family.

Patient had measles and bronchitis when 15 months old, and whooping cough at 4 years old.

Eyelids and face generally very pale and puffy. Has conjunctivitis and opacity of corneæ.

On admission—pulse 120, temperature 100°, respiration 24.

Soon after admission she passed some urine which was almost black, threw down a grumous deposit, and contained a large amount of albumen. A few hours later it was the colour of dark sherry, and, later still, quite normal.

December 1.—Urine to-day amber clear, acid, 1018. Phosphates. No albumen. I examined her heart and found reduplication of the first sound between the apex and the left border of the sternum, and a loud second sound both at apex and base.

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Pulse quick, 80 to 105, irregular in force and time; and it was difficult to judge by the finger as to the tension, but pulse tracings showed at times considerable tension. When the pulse was quick, I think probably there was some failure of the heart, and tension was not well maintained on this account.

Spleen dulness normal.

The urine of November 28 was port wine-coloured, with a grumous sediment, 1018. Contained a very large amount of albumen (about 10 or 12 parts per 1,000, Esbach). Gave hæmoglobin lines with the spectroscope, and a relation of uric acid to urea of 1 to 30.

December 2.—"The child's hands were washed with cold water at 6 a.m. After this she was well till 1 p.m., when she began to complain of pain in the hands, which were seen to be quite blue up to the level of the wrist. This blueness persisted up to 1.10 p.m., when the colour only remained beneath the finger-nails; the rest of the hands were red, puffy, and markedly swollen, but quite cold; the puffiness and redness gradually faded, and at 2.30. p.m. the hands were normal in appearance and temperature. Pulse 80, no marked plus tension during the stage of blueness and congestion. Heart first sound prolonged, second sound accentuated at apex and base. The child had marked pallor, and appeared to have intense headache during the attack in the hands, but said she did not know what was the matter, and had no headache. At 2.30 p.m. she sat up and began to play with her toys.

"Blood drawn from finger as congestion stage was passing off showed marked excess of white cells, which were actively motile and putting out many processes. Red corpuscles formed bad rouleaux, and scattered among them were collections of bright refracting nuclei about the size of one-sixth of a red cell, and it appeared as if in places the cells had burst and discharged their contents." I am indebted for the above description of an attack and the condition of the blood to the notes of my colleague, Dr. S. W. Wheaton, who was then Registrar.

December 4.—Urine of twenty-four hours, ending this morning, during which there was no attack, was 19 ozs., amber smoky, turbid, 1020, faintly acid. No albumen, some phosphates, uric acid, urea relation 1—17.

Had attacks of local asphyxia in hands or feet, or both, on December 6, 7, 8, 9. On the 11th and 12th there were no attacks, in spite of her hands being washed in cold water as before. The above attacks lasted from ten to forty minutes, and attention was

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directed to them by the child complaining of pain in the affected members. They were not accompanied by any marked rise of temperature, or followed by hæmoglobinuria, in fact, the temperature was sub-normal all the time.

December 13.—Urine of twenty-four hours, ending 8 a.m. to-day, 24 ozs., pale amber, turbid, neutral, 1016. Urea, 1·2 per cent.; uric acid, 0·04704 per cent. Relation, 1 to 25. Weight, 38lbs. Urea, 3·5 grains per pound, which, for a child of her age, is very low, and shows failure of nutrition.

Had a slight attack in the right hand at 7.15 this morning, lasting ten minutes.

December 15.—Urine of twenty-four hours, 25 ozs., pale amber, slightly acid, 1019. Urea 1·4 per cent.; uric acid, 0·05712 per cent. Relation 1—25.

Urea still very low. She is on farinaceous diet, and sister says she is always very hungry (had she been starved?). I ordered her to have meat and be fed up.[1] No doubt this low nutrition and relative excess of uric acid is the cause of all her trouble.

December 16.—Had four distinct attacks in hands and feet, first at 11.25 a.m., second, 4.25 p.m.; third, 4·50 p.m.; and fourth, 5.30 p.m. Urine passed between 9 and 11 a.m. to-day, 2½ oz., amber, turbid, neutral, 1025. Uric acid urea relation, 1—19.

Urine 11 a.m. to 1 p.m. (being a mixture of the urine corresponding to the attack at 11.25 a.m., lasting twenty minutes, with the urine of the remaining one hour and forty minutes free from attack), 1026, faintly acid; uric acid to urea, 1 to 23.

There was thus apparently less uric acid at the time of the attack than before it, but as I have pointed out in the case of headache, epilepsy, and other paroxysmal effects of uric acid, there is a variation in the excretion in both directions, a plus excretion during the attack, and a minus before or after it, or both, and when the separation is not accurate, as in slight attacks it can very rarely be, the minus excretion before or after the attack more than balances the plus excretion during the attack (which only lasted twenty minutes out of two hours' urine), and we get the result here shown, namely, that there was a greater excretion in the two hours before the attack, than in the two hours including the attack; in both periods, however, there was a considerable excess of uric acid, and

[1] I did not at this time know that meat directly introduced uric acid into the body, or I should not have ordered it, and no doubt this partly accounted for the continued excess of this substance in the urine.

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the urine is, after all, but an imperfect index of the amount of uric acid in the blood. (See p. 74.)

December 19.—Had no attack on the 17th and 18th. To-day she had an attack at 1.50, lasting only ten minutes, but followed by a rise of temperature to 102·8°, and the urine passed next after this at 5 p.m., contained hæmoglobin.

Urine passed at 1 p.m., before the attack, pale amber, slightly acid, 1,026; uric acid to urea 1—21.

Urine passed at 5 p.m. (the first after the attack), grumous red-brown, with powdery sediment, strongly acid, 1030. Hæmoglobin lines. Much albumen, but part of the turbidity clears with heat (? urates). Uric acid urea relation, 1—22. Total urea in 100 cc. was 49 grs. Total uric acid, 2·2 grs. Total acidity reckoned as oxalic acid, 5·8 grs. Relation of acidity to urea, 1—8·4, that is to say, acidity was low, and with a low acidity we had a large excretion of uric acid, 1—22. But I said above, the urine was strongly acid; how then, it may be asked was the acidity low? I reply that the urine (as is generally the case with excess of uric acid in the blood) was a very concentrated one, and the excretion of water small; hence the apparent acidity was high; but when we came to reckon the total acidity by the side of the total urea or the hourly excretion of acid in grains, we find that the acidity is relatively low, for we only find 1 grain of oxalic acid for 8·4 grains of urea, whereas my researches show that taken over a long period of time, the relation of acidity to urea is 1—6·1; 1 grain of oxalic acid for every 6·1 grains of urea, whereas here we only got 1 grain for 8·4 grains of urea, so that, as I said, acidity is really low, though, estimated only with a piece of litmus paper it would appear high. Such is the difference between exact and inexact investigation, a difference, I regret to say, not always appreciated.

What really happened in the attack of hæmoglobinuria was, I have no doubt, somewhat as follows:—At the time of the local asphyxia, 1.50 p.m., there was intense collæmia, and, an enormous excretion of uric acid in the urine, having the relation, say, 1—8 or 1—12, but in this case the attack only lasted for ten minutes, and the excessive excretion only went on probably for half an hour, but we unfortunately got no urine passed till 5 p.m., nearly three hours later. Meanwhile the temperature has risen, the alkalinity of the blood has diminished, the excretion of uric acid has fallen greatly, possibly down to 1—40 or 1—50, showing that there is no longer any excess of it in the blood, and the acidity of the urine has risen (it was possibly alkaline at the time of the attack), but the blood has

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been flooded with hæmoglobin, and this slowly finds its way out by the kidney. The result is that in the urine passed at 5 p.m. we have plenty of hæmoglobin, a low acidity, a large excretion of uric acid, 1—22, though this, in all probability, was the product of a mixture of the very much larger excretion during the attack with the very much smaller in the 2½ hours that followed it, so that the relation of uric acid is reduced from 1—8 to 1—22; just as the acidity is a mixture of the alkaline urine of the attack with the highly acid urine of the 2½ hours following it, when with high temperature there would certainly be a rise of urinary acidity, and a corresponding fall in the alkalinity of the blood.

Now that I have gone into these matters at length, I shall not require to repeat the explanation of the same phenomena in subsequent attacks.

Dr. Wheaton examined the blood one hour before an attack, and found 3,800,000 red cells per cubic millimeter; he again examined it one hour after an attack during hæmoglobinuria and found 2,990,000 cells only, a very great diminution. He repeated the examination on two subsequent occasions with similar results; and also found that the blood after the attack showed increase of white cells, and increase of coagulability.

December 20.—She had an attack of local asphyxia in both feet, lasting from 6.55 to 7.30, and followed by a rise of temperature to 99·8°. The urine passed after this, at 8 p.m., contained hæmoglobin.

Some urine passed before (? how long) the attack gave a relation of uric acid to urea 1 to 28, and that passed at 8 p.m. containing hæmoglobin, gave a relation 1—30. Here, again, I have no doubt there was an admixture of the excretion of before or after with that of during the attack, but as I was unable to obtain definite information as to the hour at which the specimen before the attack was passed, no valid conclusion can be drawn from my results. I got many such results with the uric acid headache before I found out the importance of separating carefully the urine of the attack.

December 23.—Local asphyxia in the toes of both feet 3.20 to 3.35 p.m., or lasting slightly till 4 p.m. Urine passed during the attack of a pale port-wine colour (a mixture of before and during), slightly turbid, alkaline, 1022; uric acid to urea 1—23.

Urine drawn by catheter at 4 p.m. (the end of the attack, excretion of about half an hour) dark port-wine colour, brownish deposit, slightly acid; uric acid to urea 1—28.

The remarks I made before about the effects of admixture apply here.

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On December 21 she passed some hæmoglobin at 6.15 p.m., again on the 24th at 1 p.m., and on the 25th at 9.30 a.m.; in none of these cases was the passage of the hæmoglobin apparently preceded by local asphyxia; possibly the attack escaped observation; the child was very heavy and dull in the attacks, and if other children were making a noise, her first cry of pain might not have been heard. Later, on December 25, however, 5.15 p.m., both feet were affected, and remained so for about an hour, and the urine passed at 6 p.m. contained hæmoglobin, as also the specimen next passed at 6.15 a.m. on the 26th, but that at 9 a.m. on the 26th was clear.

December 28.—She had an attack in which the left foot led the way, and was followed by the right from 5.15 to 7.30 p.m.

December 29.—The hands and feet were both affected from 5 p.m. to 6 p.m., and the temperature rose to 100·8°, but the attack was not followed by hæmoglobinuria.

December 30.—The feet and hands were affected from 3 to 3.45 p.m., and again from 5 to 8.30 p.m. The urine passed at 8.30 p.m. contained hæmoglobin, and that at 9.30 the same.

I did not estimate the uric acid urea relations in any of these specimens, because it did not appear to me that the separation was sufficiently accurate to make it worth while to do so; the attacks were slight, lasting from only a few minutes to half an hour, and in no single instance was the urine corresponding to the attack obtained separately.

In the previous more severe case of Raynaud's disease, where an attack lasted nearly twenty-four hours, there was much less difficulty about obtaining the excretions corresponding to the attack, and I got, as I have said, a relation of 1—8. That is to say, with the more severe and prolonged attack there was a greater and more continuous excess of uric acid in the blood and urine.

December 31.—Hands and feet affected from 5.15 to 7.30 p.m.

1891. January 4.—Left hand affected from 3.25 to 4.10 p.m.

January 5.—Hands and feet affected from 9.30 to 10.45 p.m.
Right hand affected from 1.5 to 1.30 p.m.

,, 6.—Hands affected from 1.30 to 2.30 p.m., and temperature rose to 99·4°.

,, 7.—Hands affected from 9.50 to 10.10 p.m.
Right hand affected from 5.10 to 5.35 p.m.
Both feet ,, ,, 6.45 ,, 7.15 ,,

,, 9. ,, ,, ,, ,, 6.45 ,, 7.45 ,,

,, 14.—Both hands ,, ,, 6.5 ,, 6.25 ,,

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January 15.—I examined the urine of twenty-hours ending 2 p.m. to-day, 18 oz.; sp. gr. 1018, and found:—Urea, 1·7 per cent.; uric acid, 0·06384 per cent.; total urea, 161 grs.; uric acid, 5·2 grs.; acidity, 15·7 grs.; uric acid to urea, 1—27; acidity to urea, 1 to 9. This shows that urea is still very low per pound of body weight for a child, acidity is low, and uric acid high; hence recurrent excess of uric acid in the blood, which is the cause of all our trouble.

She is up and going about, but seems dull and cross. Eyes still very bad.

January 17.—Feet affected from 12.5 to 12.45 p.m.

,, 18.—Both hands affected from 10.30 to 11.15 a.m.
Left hand affected from 5.30 to 6.30 p.m.

,, 19.—Feet and hands affected from 5.45 to 6.30 a.m.
Right hand affected from 5.10 to 6 p.m.

,, 20. ,, ,, ,, 6 to 7.15 a.m.
,, ,, ,, 11 to 11.30 a.m.

,, 22.—Left hand affected from 5.40 to 6.15 p.m.

On this day, as the attacks seemed to be pretty frequent, I determined to treat the uric acid, and she was accordingly put on salicylate of soda, gr. viij. three times a day after meals, and had the first dose on the evening of January 22, after the forty-second attack of asphyxia. She was also given a small dose of acid and strychnine three times a day to aid the action of the salicylate.

From this she went for twenty days right off without any attack whatever, her forty-third attack of local asphyxia occurring at 2 p.m, on February 11, while out on the roof of the hospital.

January 29.—Better and more cheerful, and all the nurses bear witness to the improvement in her temper, though her eyes are still very bad.

February 5.—Still no attack, and temper continues to improve. Yesterday, however, the temperature rose to 101·8° at 10 p.m., but there was no sign of an attack in limbs or urine.

February 11.—Attack while on roof at 2 p.m., part affected not stated.

February 13.—Feet and hands affected 11 a.m. to 1.30 p.m., was out on the roof early in the morning.

February 14.—Seems well in herself, and is singing away; salicylate mixture to be given four times a day.

February 19.—No attacks; has been on the roof twice for about an hour each time. Going on well.

February 22.—She had her forty-fifth and last attack in both

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ears from 7 to 8.30 a.m., and it is noted that her temper was very bad at the time of the attack.

February 23.—Temper is much better now than before salicylate was begun.

March 5.—Still no attacks in spite of exposure on the roof in the cold of the morning at 7 a.m. All drugs left off to-day.

She was on the roof on February 17, 18, 25 and 27 without any effect being produced.

March 9.—Weather very cold with a strong east wind, so salicylate was resumed again.

March 12.—Was on the roof at 7 a.m. to-day. Thermometer 27°F. No effect.

She now went on quite well, her temper keeping placid, and she seemed bright and happy in spite of the condition of the eyes, which remain so bad that she can only see very indistinctly, and is afraid to walk or run by herself.

May 7.—Well in herself now, but had an attack of tonsillitis about two weeks ago, for which, as another child in the ward had diphtheria, she was isolated; she, however, got quite well, and had no sequelæ.

About a week ago I put her on small doses of liq. calcis chlor. with a view of trying whether I could produce some retention of uric acid, and then, by bringing it out into the blood again, produce an attack. I, therefore, examined the urine of twenty-four hours ending this morning, and found total urea 187 grs. uric acid 7 grs. Relation 1—26. Acidity was still low, but urea had risen somewhat in accordance with the improvement in the child's general condition, being now about 4·6 grs. to the pound. It seemed, however, that with this continued low acidity I was not likely to produce much retention of uric acid, and I therefore gave up the attempt, and sent the child home.

June 22.—She still attends as an out-patient; is cheerful and well, getting fat, and has had no attack of any sort.

She had thus altogether 45 attacks of local asphyxia and 9 of hæmoglobinuria; 42 out of the 45 attacks occurred in 52 days from December 2, 1890, to January 22, 1891, and 3 attacks in 31 days, from January 23 to February 22, 1891. In the week ending January 22, the day on which salicylates were begun, she had 8 attacks, and then she went, as I have said, 20 days without an attack at all; then came 3 attacks in the next 11 days, and after that none, in spite of cold weather (as our winter certainly did not end on February 22) and exposure on the roof as before.

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The points of greatest interest to me are the pallor and headache which occurred during an attack, as described by Dr. Wheaton. The fact that her temper was generally bad, and was worse in the attacks; also that it improved when salicylates were given, to such a marked extent as to be noticed by all who saw her.

Washing her hands in cold water or exposure to cold on the patients' airing ground, the roof of the hospital, seemed on several occasions till she came under the influence of salicylates, to precipitate attacks, and I think that this is of some interest from the point of view of the possible causation of the obstruction of capillaries by colloid uric acid (see p. 149). For it seems probable that local cold may increase locally the precipitation of colloid uric acid, and that this will be more serious the greater the cold and the greater the amount of uric acid in the circulation available for local precipitation. When an attack only followed some hours after exposure to cold, it is possible that the hands never recovered their warmth and that some amount of precipitation was going on the whole time. Dr. Wheaton's observation of increased coagulability of the blood is also interesting, as the presence of colloid uric acid might to some extent account for this.

The case also illustrates fairly well the fact observed by others, that the attacks are generally in the morning; and this corresponds with the well-known fact, that the greatest excretion of uric acid in the urine, and probably the greatest collæmia, occurs in the alkaline tide of the morning; and in the morning also we are most likely to meet with that combination of urates with phosphates and alkaline salts which may induce the colloid state to make its appearance.

Dr. Wheaton says that the pulse during an attack was 80, and showed no marked plus tension.

But 80 is a somewhat slow pulse for a child of 6 years. The quickest pulse on her charts is 141, and the slowest 54, and pulses of 60, 64, and 72 on several occasions corresponded with attacks, and these show considerable bradycardia, which, as I have argued, is due to uricacidæmia (see p. 173).

As to tension, I found that it was very difficult to estimate by the finger in this case; but some tracings I obtained, show considerable tension though the pulse rate was above 80 (see *Transactions of the Medical Society*, vol. 15, p. 155, where reproductions of these tracings will be found).

Again, I think that when her pulse was quick it was not always because the tension was low, for there were several signs of heart failure here, and, as I know from observations on other cases, when

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the heart fails before high blood pressure, its systoles become imperfect (as some of my tracings from this case show) and its action quick; and Marey's law that pulse rate is inversely as arterial tension, or that the length of the ventricular systole is directly proportional to the amount of arterial resistance, holds only so long as the heart is equal to its work; and when the systoles become imperfect and the heart quickens, tension is not maintained well in spite of great peripheral resistance and obstruction of capillaries. "A long pulse means a labouring heart,"[1] but a short pulse with peripheral resistance means a failing and dilating heart.

Hannah E., age 47, admitted into the Metropolitan Hospital, April 7, 1892.

Had one child, which died at the age of five months, of "pulmonary consumption."

Had two sisters, who are well.

Had five brothers, but one is dead, and one dying of consumption; three are well.

Father died of apoplexy.

Mother, aged 66, is well.

Patient had rheumatic fever twelve years ago; phlebitis of right leg ten years ago; inflammation of lungs eight years ago; bronchitis twice since that.

Fingers have been painful and blue, with tendency to ulceration on and off for three years.

The right hand was first affected, and the left became affected in December, 1891, when she was ill with bronchitis.

The first symptom was pallor or blueness of one or more fingers, especially after washing the hands in cold water. Later on, blebs formed on the fingers, and burst.

Fingers are growing shorter and more stumpy, and are getting more painful.

Has general shivering when the attacks of coldness come on in the fingers.

A pale, poorly-nourished woman.

Temperature generally subnormal; pulse 80, irregular in force.

Heart.—Apex-beat in fifth space, just outside the left nipple-line. Blowing systolic murmur at the apex. Other sounds, nothing remarkable.

Lungs.—A few mucous râles both sides; no dulness.

Abdomen.—Nothing abnormal. Bowels tend to be constipated.

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[1] Mahomed, *Guy's Hospital Reports*, 1879.

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Urine.—Specific gravity, 1012; contains a trace of albumen. Thinks she has been passing more water of late.

Legs show dilated venous capillaries.

Right hand.—All fingers somewhat blue and shining, but the first and middle finger have a red tinge, and are somewhat clubbed, while the ring and little finger are tapering, and somewhat colder than the others.

Nails on the first and middle finger are short and have transverse striæ, the others have longitudinal striæ.

All fingers are marked with scars, which have dried up, and all are more or less painful.

Left hand.—All fingers are blue and shine, and taper from the first interphalangeal joint to the tip. All are abnormally cold and rather tender.

On the index finger there is an excoriation just in front of the nail, where a slough has separated.

The middle finger has a suppurating point under the nail, and on the last phalanx there is a bleb the size of a filbert, containing dark fluid and a slough, very painful.

The ring and little finger are tapering and cold.

All nails are curved and longitudinally striated.

Sensation is fairly perfect in all fingers.

The urine was examined on several occasions, and it always contained a trace of albumen, and had a low specific gravity.

I came to the conclusion that we were dealing with chronic Bright's disease and chronic bronchitis, dilatation and hypertrophy of the left ventricle, with or without some lesion (rheumatic) of the mitral valve, with, at the present time, some failure of compensation, shown by the irregular force of the systoles, and the somewhat rapid rate of action: and that with these conditions it was not very extraordinary that we should find what we may call chronic Raynaud's disease, with exacerbations affecting the hands. Here we have, in fact, exactly that condition which causes women to suffer from Raynaud's disease more than men, and which I shall have also to suggest further on, may be the cause of their more frequently suffering from chorea, namely, weakness of the heart muscle.

April 7.—I put the patient on nitro-hydrochloric acid and nux vomica three times a day before meals, and salicylate of soda three times a day after meals, and ordered that a tablet of nitro-

[1] Mahomed, *Guy's Hospital Reports*, 1879.

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glycerine P.B. should be given from time to time when the fingers were more than usually painful.

April 12.—Still has attacks of pain in the fingers, which turn white and blue, and get very cold. The pain in them wakes her up. Takes the nitro-glycerine tabloids, and is sure they do good; feels warmth and comfort returning to fingers about three-quarters of an hour after one.

April 13.—Pains are relieved by the nitro-glycerine. Temperature to be taken before and after a tabloid.

April 14.—Complains of coldness of left foot, the great, second, and third toes being painful and rather blue.

April 16.—Temperature in axilla ·6° up after a tabloid had relieved the pains. Observation to be repeated.

April 19.—Better; no attacks at all. No tabloids taken; fingers are less cold.

April 20.—Had an attack with a headache at 7.30 a.m. to-day. A tabloid was given at 8 a.m., and a second soon after. Got quickly better after the second tabloid. Temperature in the axilla at the time of the attack was 97·2°; when the tabloids had relieved the fingers it was 97·8°, and it rose to 98·2° in the evening.

April 27.—No attacks for several days; the slough on second finger of left hand has separated and the ulcer is healing.

May 3.—Has a headache to-day, and the fingers are colder; they were fairly warm yesterday.

May 4.—Above mixtures left off, and phosphate of soda 3ss. given three times a day in their place.

May 7.—Has an occasional headache, but the fingers are only slightly affected; no severe attacks of late.

May 9.—Had a bad headache at 11 a.m. to-day.

May 11.—Fingers very blue and cold to-day in spite of the warm weather.

May 14.—Fingers are much less blue to-day.

May 17.—Had a bad headache at 2 a.m., and the fingers are worse to-day. The index finger of the right hand is getting swollen and painful in the last phalanx. After this she soon got better, and went out.

The temperature was generally subnormal, the highest being 99·2° on the evenings of April 20 and 27, and the lowest 96·6° on the morning of April 8.

Of Raynaud's twenty-five cases, twenty were women; they were for the most part young, only one being (48) older than this patient.

One of his cases, No. 18, had mitral disease (constriction). This

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patient was worse in the spring of the year, and Raynaud mentions the autumn and spring as being the common seasons of onset.

This case also fulfils Raynaud's definition in that the troubles were to a large extent symmetrical; and like it, also, several of his cases, became chronic, lasting for years, with periods of intermission —a condition of things which he thinks is specially seen among the slighter forms of the trouble.

In the patient whose case I have just narrated above, I did not estimate the uric acid for two reasons: first, because, as I have said, her attacks were not very well marked, so that it would have been difficult to separate the urine corresponding to them; and second, because I came to the conclusion that she had Bright's disease, and there seems to be reason to believe that Bright's disease, especially in its acute stages, interferes with the elimination of uric acid, so that there may be an excess of uric acid in the blood, without any corresponding excess in the urine.

Eliza H. had hæmoglobinuria with some of her attacks, and I shall give presently the amounts of uric acid I found in the urine in other cases of hæmoglobinuria. This patient also had pallor of skin, headache, and bad temper at the time of her attacks; and when she was put on drugs similar to those I gave to Hannah E., all her symptoms greatly diminished in severity or disappeared.

In the case of Hannah E., the family history is of some interest, for her father died of apoplexy, for which we may not be far wrong in reading chronic high blood pressure, Bright's disease, and cerebral hæmorrhage; and two brothers had phthisis.

She herself had rheumatic fever, which as I have endeavoured to show, is due to uric acid, and two years later phlebitis in the leg, the relationship of which to gout is well known.

Then the troubles for which she was admitted became worse in the spring, and I have shown that in spring and summer there is a plus excretion of uric acid in the urine, the sign that an excess of it is passing through the circulation on its way to the kidney, while in the winter there is a diminished excretion with some storage of urate in the organs and tissues, the plus excretion of the warm season being the result of, and to some extent proportional to, the minus excretion of the cold (see fig. 4).

Then her attacks were often in the morning—in fact, just at the hours when in the normal physiological cycle the excretion of urate and the amount passing through the blood is greatest, and we have all the signs of its excess in the blood in the cold and pale surface, and the headaches which so frequently accompanied the attacks, and

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much the same may be said of the majority of the attacks in the case of Eliza H.

There are a few points also which I should like to draw attention to in Dr. Southey's very interesting case of symmetrical gangrene, which I was fortunate enough to see, and which is recorded in the *Transactions of the Pathological Society*, 1883, p. 286.

The patient was a girl under three years of age. It is recorded that her face and the rest of her skin presented an ashen pallor—"axilla temperature 99·4°, pulse 120, small, and a little wiry at the wrist." (She was evidently passing into the stage of reaction with rise of temperature.) Her urine was alkaline, deposited urates and phosphates, and contained albumen. There could, I think, be no doubt that this alkaline urine contained an excess of uric acid relative to urea, and that the albumen was probably due to blood changes similar to those that produce hæmoglobinuria.

At the *post-mortem*, which is interesting as adding one more to the rather scanty records of such observations (Raynaud records only three), nothing abnormal was found in the vessels of the asphyxiated parts, but the blood was everywhere fluid and "like black cherry juice."

In the discoloured parts the skin and connective tissue were chiefly affected, the muscles were only a little stained, and there was no effusion into the joints; and this is interesting, as Raynaud remarks that the lesions are more superficial than one might at first sight expect.

From the parents it was made out that there was undoubted syphilis in the father's family, and he had suffered from hæmatemesis.

The child had an attack of "febrile purpura" in October, and a feverish attack for three days from November 13 to 16.

Her last illness began on the evening of December 1 with headache. Next morning she was apparently well, but at 4.30 p.m., complained of her legs, and her father seeing bruises on them, rubbed them, which appeared to make the pain much worse, and from that time the trouble increased up to her death.

I think it quite possible that the final attack was a post-febrile rebound coming after and due to the fever of November 13 to 16, similar to the post-febrile conditions we see every day after pneumonia, typhoid, scarlet, and other fevers, with its symptoms of slow, high-tension pulse (post-febrile bradycardia), subnormal temperature, and general depression, and which are due, as I have shown, to the urate which is stored during the fever passing through

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the blood, when, with falling temperature and falling acidity, the conditions become favourable to its solution and excretion: in a word, there is post-febrile collæmia and its symptoms, and Raynaud's disease is, I believe, a mere exaggeration of some of these.

In the case of my patient Margaret C., the attack bore precisely the same relation to a previous fever, probably scarlet fever.

It may be objected that in Dr. Southey's patient the interval from November 16 to December 1 was too long to allow of this explanation, but I think it is very probable that the fever did not really come to an end quite as soon as the parents made out, and the way in which serious diseases are allowed to pass almost unnoticed among the children of the poor is familiar to us all. The first sign of this post-febrile collæmia was the headache of December 1; possibly this was followed by a little febrile movement which temporarily raised the acidity and made her appear bright and well next morning, but by the afternoon this had come to an end, and at 4.30 p.m., which comes in what I have spoken of as the afternoon alkaline tide, the full force of the uric acid storm, no doubt reinforced by the temporary fluctuation of the previous night, affected her vessels, and the gangrene began.

A glance at the plate which accompanies the description of Dr. Southey's case shows that the asphyxia affected first and chiefly those parts of the legs which in children of this age are commonly left without covering, and so are exposed to great loss of heat by radiation and conduction; so that Raynaud's argument (given above) with regard to the hands and feet will hold also in this case, for it was the skin, and not the deeper tissues that were affected (see previous remarks).

This also has an important bearing on the theory of mechanical obstruction of vessels by colloid uric acid; for if in the blood stream just as in the test-tube the precipitation of colloid increases as the temperature diminishes, one would expect to find the worst effects of such mechanical obstruction on the surfaces and extremities of limbs, rather than in the deeper and warmer tissues of their more bulky parts.

The most interesting part of Raynaud's thesis is that in which he discusses the etiology of the trouble, and sums up the arguments for and against each theory. He devotes a good deal of attention to arteritis, but sums up against it on the grounds that there is no anatomical proof of its presence, and that permanent changes in the vessels will not account for alterations in circulation which are paroxysmal and temporary. And this fact that Raynaud's disease

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is paroxysmal and temporary just like the headache, epilepsy or mental depression of which we have spoken, is of itself almost sufficient to suggest that it has a common origin with these other troubles.

Much the same conclusion is arrived at with regard to the nervous system, though he is himself more in favour of this explanation; but he points out that though a lesion of nerve structure undoubtedly influences the nutrition and sensation of the parts supplied by the injured nerve, the effect is local, and does not affect especially the circulation, while the condition he is describing affects primarily the circulation, the altered nutrition being secondary to this, and it is not entirely local, as the whole surface of the body is affected to some extent in the same way; and he finally concludes that spasmodic contraction of capillary vessels gives the best explanation, for the following reasons. The circulation in the arteries is little if at all affected in the paroxysms; the large veins are also free, and obstruction of a vein gives rise to totally different conditions from those met with in the cases he is describing. The chief point in local asphyxia is the extreme slowness with which the venous capillaries refill when emptied by pressure. In an asphyxiated finger, if the capillaries be emptied by pressure, as much as thirty seconds may elapse before they regain their colour; in a normal finger the blood will return in one or two seconds. If a ligature is passed round a finger so as to obstruct the veins, it becomes purple and congested, it is true; but if a pale spot is produced by pressure, the blood returns into its vessels even more quickly than in the normal condition. It is evident, therefore, that the obstruction is neither in the arteries nor in the veins, but in the small vessels that lie between them, and the obstruction is spasmodic, because, as in the well-known phenomena of "dead finger," it may pass away and leave no effect behind it. If, on the other hand, the spasm persists for some time, nutritional changes, which, however, are entirely secondary, will ensue. With regard to spasm, it seems at least doubtful whether the capillaries have any muscles that will produce such an effect, and in so far as it is paroxysmal it is now easy to see that it is so, for exactly the same reason that headache, epilepsy, and mental depression, are paroxysmal in accordance with the fluctuations in the causative collæmia.

There is nothing in Raynaud's argument, here quoted, against the possibility that the obstruction is mechanical; on the contrary, it is difficult to believe that spasm of any living tissue can continue so long as to cause its own death.

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Such being the etiology of the local asphyxia, let us glance at its relationship to other diseases as depicted by Raynaud.

Thus he mentions (p. 72) a case in which the blood was examined, and showed diminution of red cells and increase of white cells, and remarks that this led M. Simon to class the case under the head of leucocythæmia.

Raynaud, however, questions whether leucocythæmia is a disease at all (p. 74), but suggests rather that it is but one symptom of a blood change which has as its results, on the one hand, local asphyxia, and on the other hand diminution of red cells, increase of white cells, and hypertrophy of the spleen and glands.

I may say at once that this is a view which recommends itself very strongly to my mind, and indeed I had already (*Lancet*, 1892, vol. i., p. 663, and elsewhere), given a similar explanation of the facts before I was aware of this passage in Raynaud's thesis. And I have pointed out that in my case (Eliza H.) an examination of the blood during some of her attacks, accompanied by hæmoglobinuria, which was made by my colleague Dr. S. W. Wheaton, showed increase of white cells, diminution of red cells, and increase of coagulability; and I shall presently give my reasons for believing that these blood changes are the results of the presence of an excess of uric acid in the circulation.

It has been suggested by Dr. Hunter that the excess of uric acid which I found in the urine in these cases was the result of the blood changes, and not the cause of them; but I have given (*Lancet*, previous reference), my reasons for not sharing this opinion, and, as we shall see in the following chapter, it is easy to produce definite and distinct changes in the blood at any time by bringing an excess of uric acid into the circulation, and also that the blood itself even in physiological conditions varies from hour to hour with the amount of uric acid passing in the urine; I would refer also to some remarks by Dr. W. G. Smith in the *British Medical Journal*, 1896, vol. i., p. 1328, who points out that uric acid and xanthin are increased in leucocythæmia, while the normal oxidising power of the body is not seriously affected.

The enlargement of the spleen mentioned by Raynaud is interesting (and it was also present in Dr. Southey's case), because I have found that in nearly all conditions where the spleen is enlarged (and indeed, as I have pointed out, many others have observed the same thing), there is an excess of uric acid in the urine and in the blood, and I have been led to infer that this excess of uric acid was the result of the conditions which produced the enlargement of the

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spleen, namely, malarial and other fevers of which I shall have to speak presently; so that the enlarged spleen and excess of urates in the blood and urine may be mere modifications of that most common condition, post-febrile collæmia, which, again, is not uncommonly a cause of Raynaud's disease or allied conditions; so that the observed connection between this disease and leucocythæmia is completely explained.

The relationship of Raynaud's disease to menstruation and pregnancy is of considerable interest, though Raynaud only narrates one case in which the symptoms underwent a monthly exacerbation, and even here we are not told, as he remarks, whether the attack coincided with the period. I should myself, however, have very little doubt that this was the case, for I know of no physiological condition in which an excess of uric acid in the urine and the blood is more certain to be met with than in menstruation (see figs. 30 and 31).

As a matter of every-day observation, all conditions which upset nutrition and interfere with the taking and absorption of food at once produce a fall in the acidity of the urine and an increased excretion of uric acid; and menstruation, even when normal, and much more so when there is dysmenorrhœa, almost invariably brings about these results; and we get as a consequence of the collæmia so produced the mental depression, headache, fits, and other troubles from which women are so well known to suffer at these times. The same fact explains also why women so rarely suffer from gout till after the menopause, because this monthly plus excretion of urates prevents their stores and accumulations of the substance from becoming so large as they do in the case of men.

Raynaud, however, mentions a very good instance of the opposite effects of pregnancy; for just as menstruation lowers nutrition and increases the excretion of urates, so does pregnancy act just like meat diet, sulphate waters and many metals as a stimulus to nutrition; up goes urea and acidity, and the excretion of urates is diminished—that is, excretion falls below formation, and urates are held back and retained in the body, and with this the blood is cleared of urates and the circulation goes on freely. Now Raynaud tells us (p. 48) of a woman who noticed that the complete disappearance of her symptoms was the first indication of commencing pregnancy, and every woman knows that when she is pregnant she is well and strong, unless she has vomiting or some other complication (see remarks about figs. 30 and 31).

He says that in this case menstruation had no effect on the

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trouble. Possibly this woman had but very slight menstrual troubles, but the common effects of menstruation on the cerebral circulation are met with every day, and are too obvious to be passed over.

Here again we can explain a whole series of phenomena; for if pregnancy thus causes a retention of urates in the body, just as do most fevers and a large number of drugs, such as mercury, opium and others, about which I have written at length, when the pregnancy comes to an end, and urea and acidity fall owing to the interruption of nutrition which parturition occasions, there will be an excessive excretion of urates, the result of the previous retention, and we get what I have spoken of in the case of drugs as a rebound, not post-morphinal or post-febrile collæmia, but post-puerperal collæmia. The cause is in each case the same; the result is also the same. We get obstructed capillaries, and the results of this, slow high tension pulse, which may be irregular or intermittent; cold skin and extremities; scanty, it may be, albuminous urine; headache; mental depression, and even fits; and Raynaud (p. 130) mentions two cases of the disease as coming on after recent delivery.

Pregnancy has the same effect in epilepsy (see also interesting case of post-puerperal epilepsy in the *Lancet*, 1894, vol. i., p. 1,295), and there is a similar interesting parallel between the effects of pregnancy on Raynaud's disease, and on the dangers of chloroform (see p. 297).

See also the most interesting parallel which is here presented to us between migraine (the uric acid headache) and Raynaud's disease; for we read in Dr. Liveing's valuable work ("Megrim and Sick Headache," pp. 46-47), of a woman who inherited the complaint from her father and "became subject after puberty to severe attacks of megrim, recurring at the monthly period, generally immediately after menstruation (see figs. 30 and 31). She married at twenty and had a large family, and it is remarkable that throughout her pregnancies she had been perfectly free from the complaint, which has invariably returned after delivery."

It will be evident that we can explain completely every fact here mentioned. Both troubles are due to collæmia, and the effect of menstruation and pregnancy on this is in every case the same. But in the one patient the collæmia and the high blood pressure it produced affected especially the intra-cranial circulation and caused headache. In the other the obstructed capillaries affected chiefly the extremities, and produced Raynaud's disease.

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I can go further and say that the patient who suffered from headache had a strong heart, and consequently when the capillaries were obstructed by uric acid, had high blood pressure, of which the headache was at once the result and sign; while the patient who had Raynaud's disease had a weak heart, so that the obstruction in the capillaries was able to interfere seriously with the circulation in certain portions of the extremities; just as I shall have to suggest in chapter xvi. that the strength or weakness of the heart determines whether the same forces shall produce headache on the one hand or chorea on the other, this association with a weak heart accounting for the great frequency of the latter disease in girls, just as it here accounts also for the preponderance of girls and women among sufferers from Raynaud's disease, 80 per cent. of Raynaud's cases being as we have seen, females.

No doubt a series of anatomical and physiological, or even pathological, conditions determined in each case the locality to be most affected; but these are of little consequence, because, as I have shown, and can demonstrate at pleasure, if the blood is kept moderately clear of urates, neither kind of disturbance would take place nor continue.

With regard to irregular pulse, Raynaud mentions several cases in which this was observed, and he looks upon it as a purely nervous phenomenon. I have pointed out, however, that my pulse never falters or flutters except when I am suffering from obstructed capillaries and high blood pressure, and also that this and other "nervous" phenomena do not appear when my blood is kept free from any great excess of uric acid.

As to fevers, Raynaud mentions (p. 55) the case of a woman who had some attacks of ague in March, and about the middle of April began to be very easily affected by cold, so that exposed portions of her body became pale and then slate-coloured.

In one of my cases the attack came after a fever, and in another it came in a period of extremely low nutrition, perhaps due to insufficient food; and I have suggested that Dr. Southey's case was also due to post-febrile collæmia.

Now fever, as I have just pointed out in the parallel case of pregnancy, increases metabolism; the excretion of urea and of acid rises, the alkalinity of the blood is diminished, and as a result it is cleared of urates, and the excretion of urates in the urine is diminished to a corresponding extent; but the blood being cleared of urates, the capillaries are freed, and we get a quick low-tension pulse, as is well known. The urates are however not merely kept

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out of the blood; they are also kept out of the urine—that is, are kept back and retained in the body—and when the acidity falls at the end of the fever, out they come again, flooding the blood with an excess of urate, and producing post-febrile collæmia, with all its signs and symptoms, prominent among which are slow high-tension pulse and scanty urine; so that the relaxed pulse of fever and the tense pulse which follows it are the simple results of the altered metabolism through its effects on the quantity of urates in the blood (see p. 174.)

As I have said, Raynaud mentions what I regard as most undoubted and independent signs of free and obstructed capillaries without having himself understood their import, for on p. 99, in describing an attack, he tells us that the urine is small in quantity, and on p. 121 he says, "Quelquefois chaque accès se termine par une abondante emission d'urines."

Can anything be more simple than the explanation of this? Could anything prove more completely that obstruction of capillaries is present at the time of the attack, and is subsequently removed?

An interesting case of this disease is recorded by Mr. D'Arcy Power in the *Lancet* (1893, vol. ii., p. 249) in a girl aged 4 years and 8 months, and the patient's mother "volunteered the statement that before the attack the patient passed much more urine than usual." This diuresis no doubt corresponded with the mental well-being which in older patients is frequently noticed to precede headache or fits (see pp. 198 and 212.)

I have pointed out that under all conditions, both in physiology and pathology, the excretion of water in the urine is from hour to hour and day to day inversely as the uric acid; and that as the urate excretion can be controlled by drugs, the excretion of water can also be controlled.

I have also pointed out that it has been shown that digitalis, which is well known to contract the arterioles, does by this contraction reduce, or even completely arrest, the flow of urine (see p. 145), and have suggested that a similar obstruction of the capillaries of the kidneys by uric acid accounts for the inverse relation between water and uric acid in their excretion.

In Raynaud's disease, therefore, we have evidence not only that the capillaries are obstructed in the affected part and over the surface generally, but we also know and have evidence that they are obstructed in the kidneys in the fact recorded by Raynaud that the urine is scanty; and in the fact that the attacks may come to an end with a diuresis we have evidence that the vessels are freed or

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dilated not only in the affected area and the skin generally, but also in the kidneys.

I would also point to the interesting parallel which these facts bring out between the attack of asphyxia on the one hand, and the uric acid headache, epilepsy, and hysteria on the other. In all of these the attack is contemporaneous with a scanty secretion of urine, and is followed by more or less diuresis; and in all the results are due to the same cause: the improved intra-cranial circulation which removes the neurosis is contemporaneous with an improved circulation in the kidneys which allows of a diuresis.

But if Raynaud had investigated any of the other secretions, they would have told him the same story, for the saliva is scanty, at the same time, and for the same reason, that the urine is scanty; and I see good reason to think that the gastric juice, the bile, and the other secretions are similarly affected. Nor are we without similar evidence in respect of other organs, for in all my three cases, and to some extent also in Dr. Southey's, the headache, mental depression, and bad temper which accompanied the attacks, gave plenty of signs that the intra-cranial circulation was far from satisfactory; and in the case of Eliza H., when drugs appeared to prevent her attacks, one of the most marked concomitant signs was a very decided improvement in temper.

The fact is that in collæmia the vessels all over the body are obstructed, and all the most important organs and tissues give evidence that their functions are thereby disturbed; and the relation between Raynaud's disease and certain neuroses, such as hysteria, epilepsy, and the headache and mental depression of which I have spoken, amounts simply to this, that they are all effects of collæmia, and for this reason often occur together; and these disturbances, which seemed to Raynaud to show that the nervous system had some hand in the causation of symmetrical gangrene, merely prove that the disturbance of circulation which produces the gangrene in the extremities produces also such changes in the intra-cranial circulation that certain contemporaneous changes in the functions of the great nerve centres result.

What these changes will be depends in any given case on a variety of other general and local conditions, in addition to the collæmia which is common to all, and will vary according as the local conditions tend to favour or counteract the effects of the collæmia on the local circulation.

A most interesting case, in illustration of these remarks, is recorded by Dr. C. Crawford Aitken in the *Lancet*, 1896 (vol. ii., p.

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875), where attacks of Raynaud's disease came in association with the phenomena of uræmia.

His patient was a man, aged 43, who had a family history of gout, renal disease and epilepsy, and had himself suffered from chronic Bright's disease for six years. He had also suffered from occasional attacks of Raynaud's disease for seven years.

There were the usual cardio-vascular signs of Bright's disease, and the pulse showed increased tension during the attacks of Raynaud's disease.

The point, however, specially brought out in this paper, and it is a most interesting one, is that in five out of seven attacks of uræmic convulsions there were concurrent or closely related attacks of Raynaud's disease.

Obviously the explanation of this is similarity of causation; the obstruction of vessels which produced Raynaud's disease in some parts of the extremities caused also a rise of blood pressure or cardiac failure sufficient to produce convulsions in the manner explained in previous chapters.

Another point of great interest in Dr. Aitken's paper is the relatively low urea on the days of attacks of Raynaud's disease or convulsions, thus on days of attack the urea ran from 120 to 280 grains, and on free days from 200—320 grains.

I cannot agree with Dr. Aitken that this had anything to do with spasm in the vessels of the kidney, *i.e.*, was due to defective excretion of urea; because it was obviously due to deficient formation of urea from obstruction to the circulation throughout all the tissues of the body which I have shown does occur with every rise in the excretion of uric acid, even in physiology; and have specially pointed out in chapter viii. with reference to the causation of fatigue.

From this point of view also Dr. Aitken's careful observations of the urea are of the highest interest, for they prove, if further proof is needed, that uric acid was high in relation to urea on the days of the Raynaud's attacks, and of the uræmic fits; and we already know, from the observations of others, that urea is low during all kinds of epileptic and hysterical attacks, and rises as the attack passes off.

No doubt in Dr. Aitken's case the renal vessels were obstructed just as those of the retina which he saw, but so were also those of the liver and muscles, and the low urea was due to defective formation and removal from these.

On the other hand, if the deficient urea is due to defective elimination by the kidney, why is there not also defective elimination

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of uric acid? But in all these conditions I have shown that there is a large excretion of uric acid.

The answer is again simple. There is a large excretion of uric acid, because there is excess of it in the blood, but urea is not in excess in the blood; on the contrary it is deficient, as shown by the late Professor Semmola, in the case of Bright's disease (see chapter xiii.), and in physiological conditions we can control the excretion of urea along with the phenomena of fatigue, showing that the one depends on the other.

In the above interesting case the urine occasionally contained hæmoglobin as well as albumen.

I quite believe that there are people "whose heads have never ached," but it would not at all follow that they had never had collæmia, but rather that the conditions of their intra-cranial circulation were such that high blood pressure disturbed them but little; in others, again, the local conditions might favour circulatory disturbance by high blood pressure, and these would suffer with headache even in slight collæmia; and the local conditions giving rise to these differences of effect may be anatomical, physiological, or pathological.

Syphilis is mentioned by Raynaud as an antecedent in two cases, and there was a history of congenital syphilis in the father of Dr. Southey's patient; and this, it seems to me, is just one of those things which may so alter local conditions as to render parts previously enjoying immunity liable to the worst effects of collæmia and the high blood pressure which it produces.

Thus syphilis may produce such changes in bone membranes or intra-cranial contents as will make all the difference between collæmia and high blood pressure seriously affecting the intra-cranial circulation and hardly affecting it at all; and, similarly, in the extremities syphilis may produce such changes in the vessels as may make the difference between mere cold hands or "dead finger" and a regular attack of Raynaud's disease, the collæmia being the same in both cases.

It will be evident, then, that in claiming Raynaud's disease as an incident in collæmia, I by no means seek to exclude other factors which may both intensify the action of the uricacidæmia and determine the locality which shall suffer most.

Indeed, I think it is very probable that, as previously mentioned, the preponderance of girls and women among the sufferers from Raynaud's disease is due to their having less muscular power and activity than males of the same age; for there can hardly be any

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doubt that any weakness of the left ventricle would greatly increase the evil effects of obstructed vessels on the nutrition of the extremities.

Again, if the fits of childhood are more often due to high blood pressure in the intra-cranial cavity than to heart failure, we can understand why boys with their better muscular development and stronger hearts should more often suffer from fits than girls, so that difference of muscle power may suffice to explain the different incidence of these two diseases on the sexes.

Opium was the drug of which Raynaud made most use in treatment, and he raises the question of its action on the muscular fibres of the arterial coats, the relaxation of which is his chief object. He mentions Pott's unbounded confidence in it for the cure of gangrene, but seems to think it is of use chiefly as a narcotic.

I have shown that in conditions of collæmia and high blood pressure, opium frees the capillaries and produces diuresis by raising the acidity and clearing the blood of uric acid (see p. 54); and this action of opium causing storage and retention of urates in the body is followed, just as in the parallel cases of fever, pregnancy, and the seasonal variations in excretion mentioned above, by a rebound; and we have, as the action of opium comes to an end and the acidity falls, not a post-puerperal or a post-febrile collæmia, but a post-morphinal collæmia; and I have also shown with regard to this latter, that if the urate is removed by a few timely doses of a salicylate, the post-morphinal collæmia, with all its signs and symptoms (slow high-tension pulse, scanty urine, headache and mental depression), fails to appear. Exactly the same thing applies also to post-plumbic and post-mercurial collæmia.

In a word it can be shown that every drug which frees the capillaries and lowers blood pressure producing increased excretion of urea, rise of surface temperature, increased excretion of water from the lungs and kidneys, diminishes at the same time the uric acid in the blood and urine, conversely everything that increases the uric acid in the blood and urine produces the reverse effects, and even mere absence of uric acid from the blood and urine as the result of previous excessive excretion has the same effects on the circulation as the drugs that remove it from the blood. It is impossible, therefore, to admit that the facts prove that any one of these drugs, such as opium, has the smallest direct effect on the contractile tissues of the arterioles or capillaries, their whole effect is dependent on uric acid, and uric acid alone affects these tissues; and, as before pointed out, it is much easier to believe that uric

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acid affects the capillaries mechanically by obstructing them, than as an irritant causing spasm and contraction.

I believe that to a very considerable extent post-febrile collæmia with its results might be prevented by a similar use of salicylates during the fever (see also chapter xiii. as to their value in scarlet fever).

Here, then, we have a disease which, like those mentioned in previous chapters, is paroxysmal in relation to the more or less natural fluctuations in the excretion of uric acid, and we see reason to believe that it holds this relation, because it is due to the obstruction of capillary vessels which an excess of uric acid in the blood produces.

We have seen that Raynaud's disease affects especially the superficial structures and the extremities, and after this I need not go into any great detail to suggest that many minor changes in the nutrition of the skin are similarly related to the effects of uric acid on its circulation.

If this is so, we have at once a simple explanation of a large number of points in the cause and cure of skin diseases.

Thus the relation between erythema and urticaria on the one hand, and acute rheumatism on the other, may be explained by supposing that the skin trouble corresponds with the excess of uric acid in the blood, while the arthritis corresponds with the driving of that same uric acid out of the blood into the joints; thus it is not uncommonly seen that when a patient suffering from psoriasis develops articular gout the skin trouble disappears, and the same with rheumatism, the erythema and the arthritis do not generally originate together (see *Lancet*, 1888, vol. i., p. 523).

Again, if as we see in fig. 5, uric acid affects the circulation in the skin so much as to alter its temperature from hour to hour in physiological conditions, it is no great step to suppose that it may occasionally affect its function and structure.

Then we all know the relationship between dyspepsia and certain eruptions, or, again, between menstruation and eruptions; and in both these conditions, as I have shown, an excess of uric acid is almost certain to be met with in the urine and the blood.

Then, again, fevers are followed by post-febrile collæmia with slow high-tension pulse, mental depression and subnormal temperature, and in this condition, just as we should expect, boils and papular eruptions which are very prone to ulcerate and slow to heal are often met with, and I have myself seen quite a number of such cases after typhoid fever and pneumonia.

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Alopecia again is not a very uncommon post-febrile symptom as I have seen and read of several cases in the last few years (see *British Medical Journal*, 1890, vol. i., p. 1027 and 1239), and a case which I recently saw myself had this very suggestive connection with season, that while the hair had on several occasions grown during the autumn and winter, it had fallen off again in the following spring. After what I have said as to the seasonal variations in collæmia and the excretion of uric acid (fig. 4), I will only point out that this case of alopecia parallels in the most striking manner the uric acid headache, mental depression, asthma, and phthisis, as well as the disease we are specially concerned with in this chapter, and I cannot but think that community of causation lies at the root of this parallelism.

Then, again, we can easily understand how such drugs as acids, opium, the iodides, calomel and thyroid gland or extract (Dr. Davies, *Lancet*, 1893, vol. ii., p. 399) act in curing these skin diseases, for all these substances have this one point in common, that they clear the blood of uric acid (see chapters iii. and iv., also *British Medical Journal*, 1888, vol. i., p. 27, and 1892, vol. ii., p. 165, and *Lancet*, 1888, vol. ii., p. 63).

And as I have said, I have for some time been in the habit of treating skin troubles originating in connection with any of the above-mentioned disturbances of nutrition with drugs which clear the blood of uric acid, and I think with considerable success.

Then if the vessels of the skin are obstructed by uric acid so that surface temperature is reduced and even the nutrition of the skin is eventually affected, it is probable that in those capillary vessels where the circulation is absolutely at a stand, the very walls of the vessels themselves will suffer in their nutrition and deteriorate, so that when the blood again passes into them they may bulge and leak, and thus small extravasations of blood result.

If this is the explanation of purpura it almost amounts to a demonstration that the action of uric acid on the capillaries is not that of a mere irritant on a living tissue, for it is hardly possible to believe that any tissue could keep up a spasmodic contraction while its substance is actually being disintegrated.

In this way I think purpura may be connected with uric acid, and the changes it produces in the circulation, and this will explain its connection with the rheumatic group, and also with chronic Bright's disease, dyspepsia, post-febrile conditions, and menstruation (see *British Medical Journal*, 1890, vol. i., p. 596, and *Lancet*,

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1891, vol. i., p. 658, and 1891, vol. ii., p. 933, and *British Medical Journal* epitome, May, 1893, p. 80).

We have seen that Raynaud did not favour the idea that the troubles he described were due to local nerve lesions or neuritis, though it is still held by some to be due to disease of trophic nerves or their centres,[1] but probably the only relation between Raynaud's disease and neuritis is that both may be due to uric acid (see also Dr. Buzzard's opinion in the *Lancet*, 1893, vol. ii., p. 1233). I have myself also heard from Dr. Mackie, of Lowdham, Notts., and others, of cases of neuritis which evidently had important connections with uric acid.

Theoretically it seems possible that one may get a connection between peripheral neuritis and the action of uric acid on the tissues and circulation in two ways, first as a gout of the fibrous tissues in and round a nerve bundle causing pressure, irritation and degeneration, such as occurs, for instance, in sciatica, or possibly also in herpes zoster, and the action of alcohol, arsenic, and several metals in producing these troubles may simply be their effect in driving uric acid out of the blood into the fibrous tissues that support the nerve fibre. Second, in conditions of Raynaud's disease similar to those described above there will probably be more or less alteration of nerve structures in and around the lesion, but these are entirely secondary to the circulation changes as Raynaud himself points out (previous reference).

Some points of interest have been brought out by recent writers especially with regard to the treatment of skin troubles, chilblains, pruritus, etc., by calcium chloride, a drug which undoubtedly clears the blood and urine of uric acid while it is being taken (see Dr. Savill, *Lancet*, 1896, vol. ii., p. 300).

The relationship of psoriasis to menstruation, pregnancy, and the spring season, and to gastro-intestinal irritation, all points I have already mentioned are further illustrated, though mixed with what I regard as erroneous pathology, in an article in the *Lancet*, 1895, vol. i., p. 1422.

I have also had a letter from Dr. H. S. Purdon, of Belfast, pointing out that he has long been in the habit of reducing animal food in psoriasis with great benefit, and quoting a paper read at the Dermatological Congress of London, by Dr. Bulkley of New York, advising this treatment.

The only indication for the treatment of this group of diseases is

[1] See Dr. Sharkey, *British Medical Journal*, 1896, vol. i., p. 456.

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to clear the blood of uric acid as quickly and as completely as possible.

For this purpose mercury or its iodide, opium and the nitrites, or ammonium, are likely to be the most useful drugs, and as regards diet it will be as well not to administer any uric acid that can be left out without injury to nutrition, and so to avoid such things as soup, beef tea, and meat extracts, strong tea or coffee, and we must bear in mind that milk diet lowers blood pressure by keeping the blood clear of uric acid, which is what we want to do in Raynaud's disease. With regard to skin diseases the same drugs are of use, and salicylates are also sometimes of great value, and calcium chloride, or iodide of potassium, are drugs which act in the same way, and are mentioned in some of the experiences quoted above: but diet alone goes to the root of the matter by eliminating and keeping out the cause.

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CHAPTER XII.

Paroxysmal Hæmoglobinuria and Anæmia.

It was the clinical observation of cases of paroxysmal hæmoglobinuria and certain special forms of anæmia that first suggested to my mind the possibility that these troubles, as well as anæmia, might be due to the presence of excess of uric acid in the blood.

I shall first of all, therefore, mention some of these cases and the results I obtained by investigating them.

December, 1888.—John H. McL., age 4 years and 10 months, said to be subject to attacks of cold and shivering, in which he passes red water.

Is generally extra well for some days before the attack, but his bowels are constipated (extra well means retention of uric acid; note the parallel here of what occurs in the headache and epilepsy of uric acid).

Just before the attack he yawns a great deal (collæmia).

His water on the day after the attack is quite clear again.

December 10.—His mother brought him to my out-patients' room to-day saying that he has an attack coming on. Has been taking cod-liver oil and steel wine for the last week. Was this a rebound after the iron?

He is pale and his hands and forearms are cold. Seems dull and heavy, shivering (?). Pulse slow.

I told his mother to sit in front of the fire with him; and in half an hour, at 3 p.m., she came back with the child, and brought some reddish urine he had passed. His face was flushed, and he seemed dull and heavy and said he had a headache; pulse now quicker. His mother says his bowels have not been open for two days. He does not get these attacks unless he is exposed to cold in some way. Have we here a condition in which cold acting with other causes just as in Raynaud's disease precipitates or greatly increases collæmia?

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The specimen of urine was reddish-brown, clear, 1024, showed the spectrum of oxy-hæmoglobin, and also that of acid hæmatin, the latter being removed by addition of ammonia. Under the microscope numerous pigment granules, some epithelium, fairly numerous shadowy blood cells, also numerous granule and pigment, speckled casts. No oxalates. Urine, after boiling and filtering, gave urea 1·5 per cent., and uric acid ·06048 per cent. Uric acid to urea 1 to 15. There was, therefore, an excessive excretion of uric acid, and probably as the child did not pass water before the attack began this was a mixture of the urine in the bladder before the attack, with that excreted during the attack, or the uric acid would have been higher still.

With regard to this case, I have very little doubt that it was a uric acid storm. He was extra well for a day or two before the attack, just as in uric acid headache and epilepsy (retention). The attack itself comes at a time—3 p.m.—when there is normally a plus excretion of uric acid (second, or afternoon alkaline tide, see fig. 1); all the signs and symptoms of the attack are those of collæmia; and lastly, in the blood-stained urine itself we find excess of uric acid. Unfortunately, this child never returned again, so that I could not investigate the matter further.

For comparison with this, I will now give a few notes of the case of a member of our profession, who consulted me on account of uric acid headache.

May, 1888, G.F.T., age 33.—In practice in a Midland county; works hard, lives plainly, fair amount of exercise and riding, occasional hunting. Father has slight attacks of gout, mother rheumatic and two years ago had peliosis rheumatica.

Previous health.—Slight rheumatic fever nine years ago; occasional joint pains since that; four and a-half years ago had rigors and dyspnœa, and was ill three months. Has always suffered from headache, but worse the last four years, sometimes now one every week. He has the pain on waking in the morning, and it remains the whole day. Taking wine at dinner always gives a headache next morning. His pulse, as observed by his assistant, is slow and of high tension during the headache. He suffers also from depression and irritability, and has cold extremities and rigors during headaches.

Here there is a strong family history—gout on one side and rheumatism on the other, and nearly every possible sign of excess of uric acid in his own blood or joints. And now we come to the part that bears upon our subject. Also occasionally when he gets

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cold he has a rigor and a temperature of 102°, sometimes with joint pains, and passes smoky urine. In the autumn of this year he had such an attack after being out hunting and getting cold, and he kindly sent me some of the urine; unfortunately the notes I have of its examination are not very precise, and I was only able to examine it forty-eight hours after it was passed. It was acid, contained a slight excess of uric acid, fairly numerous blood-cells and some oxalate crystals, and gave the oxy-hæmoglobin spectrum. He himself considered that these were attacks of paroxysmal hæmoglobinuria, but I do not attach great importance to my examination because the urine was not fresh, and I think that the oxalates were possibly formed out of uric acid and diminished its apparent quantity.

Compare also a short note of a case that came to Dr. Brunton's out-patients' room at St. Bartholomew's, which he kindly allowed me to examine. April 25, 1890, Edward W., age 35.—The case was diagnosed as paroxysmal hæmoglobinuria, and I was given a small specimen of the urine and took a tracing of his pulse; its rate was 112, and yet, in spite of this, the tracing showed considerable tension, as the predicrotic wave was fairly well marked in the down stroke, the predicrotic notch was a considerable distance above the base line, and the dicrotic wave only of moderate size. The second sound of the heart was markedly loud. We were here probably just at the end of the cold stage and the beginning of the fever.

The urine was like pure blood, but showed no blood discs under the microscope, and after removal of albumen it yielded urea 1·4 per cent., uric acid ·12768 per cent.; relation 1—11—an enormous excess of uric acid, and a relation to urea which it may be said is never met with in health.

I will here also mention a case which, more than any other, opened my eyes to the probability of uric acid producing destruction of red cells and so anæmia.

July, 1889, a lady, age 46.—A patient under the care of Dr. Brunton, during whose absence from home I saw her. Had a gouty family history, but never had gout herself.

She complained that she had "anæmic attacks" which she was sure were connected with gout. She had lived a healthy outdoor life, and often played cricket with her children, now growing up.

Her face was tanned by exposure to the sun; but through this and also in tongue and gums there was every sign of intense

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anæmia; I felt sure that she must have had a hæmorrhage, and suggested loss of blood by piles—which she had to a slight extent—or by excessive menstruation; these, however, she denied, and maintained that she had suffered off and on from this anæmia, which came in attacks, and was in some way connected with gout. So far as I could make out from her description, the attack after which the anæmia appeared was of the nature of a bilious attack, or sick headache; but she had no hæmaturia. Have we here hæmoglobinæmia not sufficient to cause hæmoglobinuria, but perhaps lasting over a longer time and producing the intense anæmia which I saw?

This, of course, raised in my mind the question, is collæmia a cause of more or less destruction of red cells, and does it in this way bring about more or less chronic and recurring anæmia? And having once been led to regard anæmia from this point of view, I was not long in coming on what have appeared to me to be other signs of the possible production of anæmia by uric acid. I have also pointed out in my previous writings that the injection of creatinin into the blood had been shown to produce destruction of red cells (*Comptes Rendu de la Soc. de Biologie*, 1877).

Aug. 12, 1890, Daniel H., age 10.—Admitted under my care in the Metropolitan Hospital. Complains of pallor, sleepiness and pains in the head. Father and mother well, five brothers and sisters well. Jaundice as an infant; measles also as an infant. Had a pain in his head on Aug. 1, and a pain in his right side on Aug. 7. Pallor gradually increasing but much worse the last two weeks.

Is now poorly nourished and pale even to bloodless. The conjunctivæ have a slight lemon tinge. Appears intelligent, but is dull and depressed. Pulse 120. Temperature 100°. There is a systolic murmur all over the cardiac area. The spleen is greatly enlarged, the notch being felt at or below the umbilicus, and the lower edge is level with the anterior superior spine of the ilium. Blood shows increase of white and diminution of red cells. He was given liq. arsenicalis ♏iii., to be gradually increased. During my absence for a holiday he came under the care of Dr. Rolleston, who increased the arsenic to ♏viii. and eventually to ♏xii. and added a little digitalis, and on Sept. 17, pil. ferri carb., gr. v., was given twice a day.

On my return in the fourth week of September the child was worse than when admitted; he was not only very pale, but was weak and hardly able to sit up in bed. I got a specimen of twenty-

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four hours' urine and found it to contain a great excess of uric acid, 1—13·8, and this suggested to me that his dulness and general misery were due to collæmia, which no doubt he had to a very serious extent, even if the severe anæmia was not also due to it; at any rate I felt that I knew nothing about the causation of splenic leucocythæmia, and would therefore treat the collæmia, for which I might be able to do something (see also p. 367).

On Sept. 26, the note of the house physican, Dr. Stanley, was: "Still has some pain; extremely anæmic; spleen if anything, larger. Hands always tremulous. Pulse 126."

Sept. 30, I found him in the same condition lying weak and dull in bed. I accordingly stopped all the previous drugs, and gave a mixture containing ♏x. of dilute nitro-hydrochloric acid three times a day before meals, and another mixture containing sodii salicyl. gr. x., sp. am. arom. ♏xv., three times a day after meals, with the object of affecting the collæmia.

Blood examined to-day (that is, before treatment) shows 10 red and 1 white cell to a micrometer square. Blood examined by Dr. Stanley.

Oct. 7.—Dr. Stanley's note is: "Colour much improved, less tremulous." And this was the beginning of a steady and continuous improvement, so marked and so unexpected as to surprise all who saw him.

Oct. 14.—Weight 3st. 11lbs. Abdomen 25½in. at umbilicus.

Oct. 20.—Blood much better in appearance, shows 35—40 red cells per square.

Oct. 21.—Bright and cheerful; up and about, and goes out. Has some colour in face now. Weight 3st. 13¼lbs. Spleen (?) smaller.

Oct. 29.—Weight 3st. 12lbs. 13ozs.

Oct. 31.—Spleen smaller and more to the left; the notch is now one finger-breadth above the umbilicus. Abdomen 24½in. at umbilicus.

Nov. 12.—Continued improvement, same drugs. Weight 3st. 13lbs. 2oz. Spleen same.

Nov. 14.—Blood 23 red and 1 white cell per square. All medicines suspended.

Nov. 18.—Weight 3st. 13lbs.

Nov. 26—Acids and salicylate begun again.

Nov. 29.—Red cells 35 per square. Splenic notch two fingers' breadth above umbilicus.

Dec. 6.—Red cells 29 per square. Pil. ferri. carb., gr. v., given twice a day in addition to other drugs.

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Dec. 13.—Red cells 45 per square.

Dec. 17.—Weight 3st. 12lbs. 6ozs. Going on well; seems bright. Abdomen at umbilicus 23in.; spleen much smaller.

Dec. 20—Bright and well. Red cells 37 per square.

Jan. 17, 1891.—Same treatment continued. Red cells 38 per square. White cells not in excess, only one or two in the field. Weight 3st. 13lbs. 10ozs.

After this he continued very well and was allowed to go home.

I am aware that cases of splenic leucocythæmia have improved on various treatments, or have got well in spite of treatment; but the result in this case followed so immediately on the alteration of treatment as to impress all who saw the case with the belief that it was not a coincidence merely.

Since this I have seen several cases of severe anæmia in young women, which resisted iron given in the ordinary way (generally pil. ferri. carb. in increasing doses) for several months; but improved at once and decidedly on a course of salicylate of soda; and this drug has always seemed to affect their spirits and general condition in a remarkable way, leaving no doubt in my mind that they had been suffering from severe collæmia.

With regard to the way in which the salicylates produced this improvement, I shall have something to say when I come to demonstrate my curves, and similar treatment apparently prevented attacks of paroxysmal hæmoglobinuria and Raynaud's disease (see p. 358).

Lastly, I was led to notice, as the result of my previous experience, that, in a large number of cases of chlorosis or anæmia in young women, more or less dyspepsia, or even a bilious attack, as in the lady above mentioned, occurring especially at the menstrual periods, held an important place in the history of their trouble, and I knew well that these gastric disturbances meant a fall in urea formation and excretion, a fall in the acidity of the urine, and a corresponding rise in the alkalinity of the blood, so that this fluid at once became a better solvent of uric acid and its compounds, and at once took them up in solution from all points of deposit in the body. (Liver, spleen, fibrous tissues and joints.)

In a word, the dyspepsia produced collæmia, and everything seemed to make it probable that the collæmia produced the blood destruction and anæmia.

Then, in the case of Raynaud's disease, with paroxysmal hæmoglobinuria, the notes of which are given in the previous chapter, my colleague, Dr. S. W. Wheaton, kindly examined the blood, and found on several occasions, corresponding with the

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hæmoglobinuria attacks, a diminution of red cells, an increase of white cells (see p. 355), and an increase of coagulability.

Dr. Wheaton has also given (*Transactions of the Pathological Society*, vol. xlvi., p. 168) an interesting account of the pathology of the "Blackwater" fever of West Africa, which appears, as he shows, to have many points of resemblance with paroxysmal hæmoglobinuria; and I should have little doubt that it represents the effect of severe malarial fever on the excretion of uric acid, and so indirectly on the blood (see p. 174 and 364), and it is interesting to note that malarial fever is known to be a cause of "lithæmia" (see my paper in *Brain*, 1891, p. 73), and of Raynaud's disease.

For a case where hæmoglobinuria accompanied an ordinary attack of benign intermittent fever (see *British Medical Journal*, 1896, vol. i., p. 590). Yet Dr. Manson seems to think that hæmoglobinuric fever is caused by a different parasite.

There thus seemed to me to be a considerable accumulation of facts tending to show that in paroxysmal hæmoglobinuria, splenic leucocythæmia, chlorosis, and anæmia, there is at the time of the blood deterioration a considerable excess of uric acid, both in the urine and in the blood; in the urine I have found it in excess, and in the blood it gives rise to signs and symptoms which are practically identical with those of the uric acid headache (see chapter vi.).

Then, again, in several of these disease conditions, a drug (salicylate of soda), which eliminates uric acid, and prevents its being present in excess in the blood, appears to produce more or less marked improvement, even when iron or arsenic have failed, while dyspepsia, which brings excess of uric acid through the blood, does harm.

At this point in my investigation the writings of Horbaczeuski, and a lecture by Prof. A. E. Wright, were published, and I therefore said in a letter to the *Lancet*, 1892, vol. i., p. 663, that it appeared to me that these investigators were really mistaking a cause for an effect; and I gave my reasons for thinking that the excess of uric acid which they noticed in the blood and urine at the time of certain blood changes was the cause of those blood changes, and could not well be their effect.

I said further that in the case of paroxysmal hæmoglobinuria, it could be proved that the excess of uric acid in the blood and urine at the time of an attack was not the result of the blood changes because it was the result of a fluctuation in urate excretion (minus excretion or retention) which began hours before there were any blood changes.

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In this respect also the excess of uric acid in paroxysmal hæmoglobinuria has an identical causation with the excess in the paroxysmal headache, the paroxysmal fits, and the periodical mental depression described in previous chapters; and in all these alike the fluctuation in the excretion of uric acid is the cause of all the signs and symptoms, and not their result.

At the time my paper on a case of Raynaud's disease was read before the Medical Society (see *Transactions*, vol. xv., p. 156), Dr. Hunter, whose investigations on the blood are well known, said: "In a number of the diseases of the blood of a destructive nature, such as leucocythæmia and pernicious anæmia, the uric acid was greatly increased; there was evidently a direct connection between the two, and he felt sure that the appearance of the uric acid was a result, and was not to be regarded as standing in a causal relation to these diseases." I am glad to see that Dr. Hunter is at one with me as to the facts, and further considers that there is a direct connection between them; but I hope presently to be able to demonstrate that the connection is just the reverse of the one he suggests.

All these facts then seemed to render it very probable that uric acid was the cause of these blood changes both in paroxysmal hæmoglobinuria and anæmia.

But I have complete power over the excretion of uric acid in the urine, and if anyone will chalk out a curve on the wall which he wishes his urate excretion to follow from day to day, I will undertake to make it follow a very similar curve, provided he follows my instructions as to diet and drugs that affect the solubility of the substance.

But the excess of uric acid above the relation to urea of 1—35 represents, I believe, the amount of uric acid that passes through the blood each day; thus when the uric acid curve is above the urea curve by two or three grains, two or three grains passed through the blood that day (see chapter iii.).

It follows that if I have complete power over the curve of excretion I have also complete power over the amount that can pass through the blood, and if uric acid causes the above mentioned blood changes I ought to be able to produce, if not an actual attack of paroxysmal hæmoglobinuria, at least such blood changes as occur in anæmia.

But we have seen in chapter iii. that uric acid taken pure by the mouth passes straight into the blood (which was to some extent known before), and will in due time pass out in the urine in quantity which is roughly proportional to that swallowed.

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The only essential condition of this direct absorption and excretion of uric acid is that the blood shall be kept in such state as favours, or at least does not hinder, the solubility of urates; and this can be fulfilled by so ordering the diet as to prevent the alkalinity of the blood being diminished.

It is thus possible to increase the uric acid passing through the blood by the simple process of administering it pure (in powder grains 1—2 ter.) by the mouth; leaving diet and all other factors unchanged.

But those who have from diet and other causes but a slightly alkaline blood must not expect to increase the uric acid it contains very much by taking it by the mouth, for though it gets into their blood it will quickly be driven out again into their fibrous tissues and organs where it will remain till the blood becomes favourable to its solubility.

And in no one (unless the blood is very alkaline) will there be much excess of uric acid in the blood and urine on the day a dose of uric acid is taken, because uric acid itself diminishes the alkalinity of the blood, and interferes for a time with its own solubility; but on the second or third day after a dose when the alkalinity of the blood has again risen uric acid will begin to be present in excess in the blood, and to pass in excess in the urine, and such excess will correspond more or less in extent and duration to the dose taken (see also *Journal of Physiology*, vol. xv., p. 167).

Our problem then is this. Many disease processes in which there are important blood changes appear to be contemporaneous with the presence of an excess of uric acid in the blood and urine, and there are reasons for supposing that the uric acid may be the cause of the blood changes: does the intentional production of an excess of uric acid in the blood bring about any similar blood changes?

On this point I shall allow my curves to speak for themselves with such small explanation as may be necessary.

Before giving them I will say that I have used for this investigation the hæmoglobinometer and hæmocytometer of Dr. Gowers, and have followed as closely as possible the directions issued with the instruments.

The blood decimal is the result of the fraction $\frac{\text{per cent. hæmoglobin}}{\text{per cent. red cells}}$ or if normal $\frac{100}{100} = 1{\cdot}0$, and all smaller quantities are represented by decimals as in the following curves; and I agree with Dr. A. E. Garrod, Dr. Wilcox, and others (*Proceedings of the Royal Medical and Chirurgical Society*, February 9, 1892), that this is the safest

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guide to the condition of the blood, representing as it does the hæmoglobin value of the individual cell: for the absolute quantity of cells and hæmoglobin varies greatly according as the blood is concentrated by diuresis, or is diluted by retention of fluid in the body,[1] but these things cause no variations in the value of the blood decimal, which again can easily be represented in a curve, for comparison with the curves of the urate excreted in the urine.

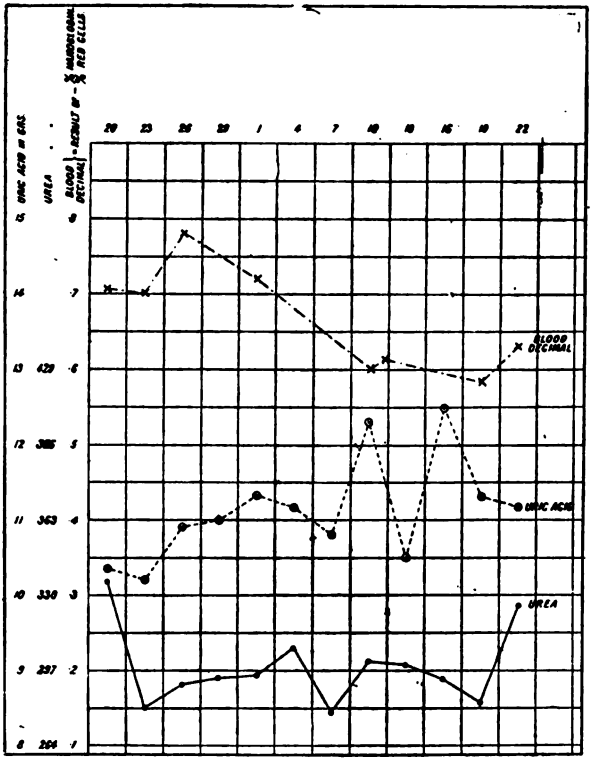

FIG. 43.—CURVES OF URIC ACID EXCRETION AND THE BLOOD DECIMAL.

Fig. 43 represents the results of simultaneous examination of the blood and urine in myself, the blood being examined only every two or three days, and the urine curves being obtained by dividing the total excretions of three days by three so as to shorten the figure.

Notice here the general downward direction of the blood decimal

[1] See *Journal of Physiology*, vol. xiii., and *Lancet*, July, 1892.

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curve and the general upward trend of the uric acid curve. The urea curve is given simply to show the height of uric acid above urea (the curves are super-imposed at the relation of 1—33) as the index of the probable amount of uric acid passing through the blood.

On May 20 at the beginning of the figure, urea is close to uric acid so that little or no uric acid passed through the blood, and the blood decimal is fairly high = ·71. On May 23 uric acid exceeds urea by 1¾ grs., and this amount probably passed through the blood, and with this the blood decimal falls to ·70. On May 26 more than 2 grs. of uric acid passed through the blood, and yet the blood decimal rises decidedly to ·78, but the explanation of this is probably that the blood was not examined sufficiently often to correspond with the excretion curves, for uric acid was low on two days preceding the 26th, while a high rise on the 26th brought up the average in the blood for three days to 2 grs. per day. If the blood had been examined on the 25th, it would probably have been found above ·8, a fall to ·78 taking place with the high uric acid of the 26th. The blood is again examined on June 1, the uric acid in it averaging meanwhile 2 to 2¼ grs. per day, and with this there is a fall to ·72. On June 10, with uric acid rising to 3¼ grs. per day, there is a marked fall of the blood decimal to ·6; there is a slight rise on the 11th, corresponding to a fall of uric acid; and a fall of the blood decimal to ·56 on the 19th in accordance with the passage of 3 to 3½ grs. through the blood on the days from the 16th to the 19th. Lastly, we see a rise of the blood decimal to ·63 on the 22nd with a fall of the uric acid passing through the blood to 1¼ grs. per day.

This figure shows generally that the blood decimal is higher, the nearer the uric acid is to urea, *i.e.*, the less there is passing through the blood; and lower the higher the uric acid is above the urea, *i.e.*, the more there is passing through the blood.

The high rises of uric acid on the 10th, and again on the 16th were due to uric acid taken by the mouth on purpose to increase the amount passing through the blood.

Fig. 44 shows similar curves of results obtained on myself, the blood being examined every day.

On the 23rd, uric acid exceeds urea by 1½ gr. and the blood decimal is at ·59. On the 24th, uric acid exceeds urea by 2¾ grs. and the decimal falls to ·53. On the 25th, the uric acid exceeds urea by 1½ grs. only, and the decimal rises to ·62. On the 26th, uric acid exceeds urea by less than 1 gr., and yet the decimal falls to ·56, but it rises next day to ·63, uric acid remaining still about 1 gr. above urea. On the 28th, with a rise of uric acid to 1⅓ gr. above

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urea it falls to ·58. Then on the 29th, it rises to ·65 in spite of uric acid being $1\frac{1}{2}$ gr. above urea, and it remains at ·65 on the 30th, uric acid being still about $1\frac{1}{2}$ gr. above urea.

On July 1, I tried an experiment, taking xlv. gr. of sodii salicyl, with the object of bringing a lot of uric acid through the blood, and in this I was successful, as uric acid exceeded urea by nearly 7 grs.;

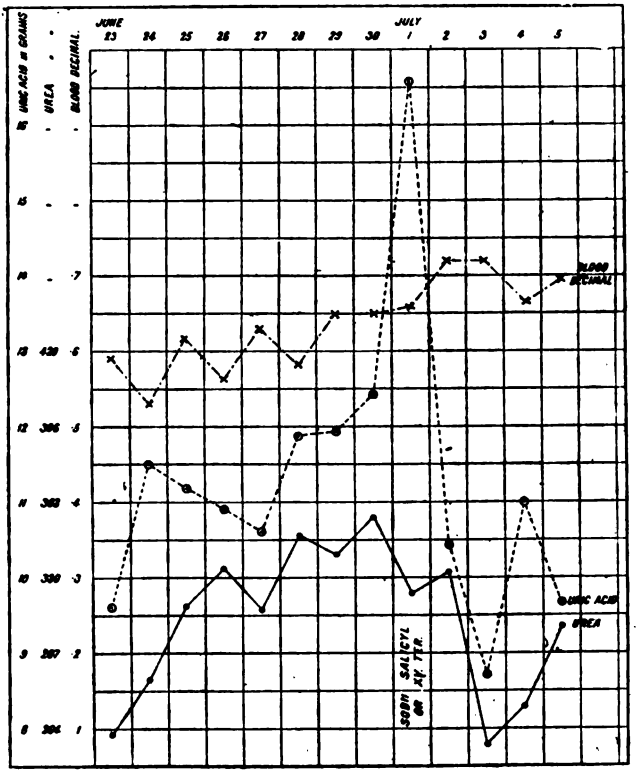

FIG. 44.—CURVES OF URIC ACID EXCRETION AND THE BLOOD DECIMAL FROM DAY TO DAY.

but the blood decimal did not fall, indeed it rose slightly to ·66. On July 2, uric acid fell close to urea, as the salicylate was left off, so that by hypothesis none passed through the blood; and with this the blood decimal rose to ·72 and remained there on the 3rd, though uric acid was about $\frac{3}{4}$ grain above urea. On the 4th, however, uric acid rose, being $2\frac{3}{4}$ grs. above urea, and with this the blood decimal

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fell to ·66. On the 5th, uric acid fell again, being scarcely ¼ gr. above urea, and with this the blood decimal rose to ·69.

The exceptions mentioned above only serve I think to show up the rule that uric acid, in relation to urea and the blood decimal, move in opposite directions. The exceptions are probably due to want of exact correspondence between the examination of the blood and that of the urine. The urine of the given date is the excretion of the 24 hours ending 7 a.m. on that date, while the blood was examined at 11 a.m. each day. It is quite possible that a large amount of uric acid passing through the blood between 7 and 11 a.m. may depress the blood decimal more than the excretion of the previous 24 hours would lead us to expect, or a small excretion in those same hours might allow the blood to recover a little from the uric acid of the previous day.

That salicylate of soda could bring so much uric acid through the blood without depressing the blood decimal was rather a surprise, but I would point out that these large excretions under salicylates are not accompanied by the usual symptoms of collæmia. There is no headache, and but little mental or bodily depression, though if seven grains of uric acid had passed through the blood in combination with an alkali, there would have been severe headache, marked mental and bodily depression, slow high tension pulse and scanty urine, and with these probably a marked fall of the blood decimal. (As in the case of the lady mentioned above.)

The rise of the blood decimal with the low uric acid the day after the salicylates is extremely interesting and illustrates probably the way in which these drugs did good in the case of splenic leucocythæmia mentioned above, and in several cases of simple anæmia and chlorosis in which I have also used them, when iron did not seem to act well; for, as we shall see presently, uric acid is more powerful than iron, and when both are present in the blood together, its decimal falls instead of rising.

It seems probable then that the good effects of salicylates are due to two things; first, that they rapidly clear urates out of the body without allowing them to do harm in passing through the blood; and second, that they thus, by elimination, free the blood from uric acid and allow the blood decimal to rise.

In watching the blood decimal curves over long periods of time, as I have often done, and as is shown incidentally in fig. 65, I could not help noticing what I have mentioned above, that now and again where the uric acid had been low in the previous 24 hours the blood decimal had perhaps not risen as much as one would have expected,

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or on the other hand, when uric acid had been high it had not fallen as much as seemed likely from previous experience, and noting these slight variations led me to examine the relations of these curves to each other over shorter periods of time every few hours.

And as soon as this was done the cause of these slight variations became apparent, for I found that the blood decimal really varied from hour to hour with the uric acid passing in the urine, hence a large rise of uric acid at the end of the 24 hours period would

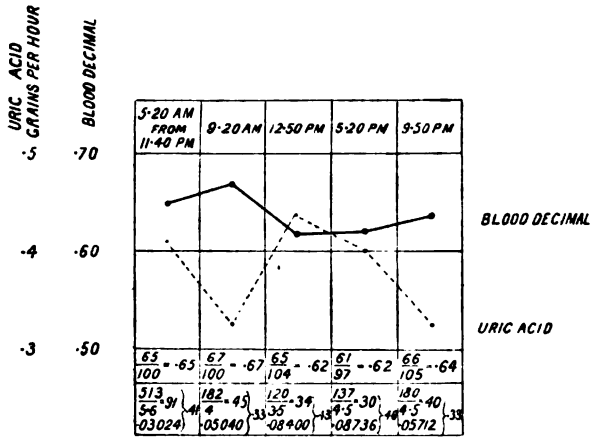

FIG. 45.—CURVES OF URIC ACID EXCRETION AND THE BLOOD DECIMAL FROM HOUR TO HOUR.

depress the blood decimal more than the 24 hours curve would lead one to expect, or on the other hand, a large fall of uric acid for a few hours would cause the decimal to rise in spite of a large excretion of uric acid during most of the previous 24 hours.

Now the curves in fig. 45 are given to illustrate that point. They do not show quite normal curves, either of uric acid excretion or the blood decimal, for uric acid is generally high at 9 a.m. and lower at noon and 5 p.m., and the blood decimal is generally low at 9 a.m., rising again towards 1 p.m., but these curves do show exactly what I want to point out, that when the uric acid excretion is unusually small in the morning hours, the blood decimal is unusually high, and when the uric acid is unusually high in the middle of the day the blood decimal falls instead of rising.

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Again, if there had been only one examination of the blood decimal, say at 9.20 a.m., it would have appeared too high, because there had been a large excretion of uric acid in the previous twenty-four hours, but examining more closely we see that on this particular morning the uric acid excretion fell very much from 5.20 a.m. to 9.20 a.m., and so the blood decimal rose above its usual level at those hours, and also above what one would have expected from the excretion of the previous 24 hours as a whole.

The figures below the curves in fig. 45 are 65 per cent. hæmoglobin, over 100 per cent. of cells = the resulting decimal ·65, and below these 513 the total urine in cc. divided by 5·6 the time and giving a resultant 91 cc. per hour; below these is ·03024 the percentage of uric acid in the urine, and this × by 91 = ·41 grs. of uric acid per. hour, as indicated in the curve.

As a rule the uric acid is high in the a.m. hours, falling towards 1 or 2 p.m. (fig. 3) rising again slightly later in the afternoon, and falling again in the evening and early night hours. And the normal blood decimal curve is low in the a.m. hours, rising towards 1 p.m.; falls again slightly in the later afternoon hours, and rises again in the evening hours, in which respect the curves in fig. 45 are nearly normal.

But the uric acid in these curves is practically under complete control, and being altered from hour to hour at pleasure the blood decimal will follow, so that any desired curve of the blood decimal can be produced, and I am so confident that the results obtained are constant and reliable that I will undertake to alter the blood decimal curve of anyone in either direction, or if I am allowed to examine the blood of anyone every two or three hours I will undertake to tell correctly the chief variations in the excretion of uric acid in the urine over the same periods.

I shall now go on to my other figures, showing some of the results I obtained in cases of chlorosis by causing excess of uric acid to pass through their blood.

In these cases the urine was not collected, but no doubt the effects on excretion were the same as in my own case, and the administration of uric acid in one form or another always produced, as we shall see, immediate and distinct effects on the blood decimal.

Fig. 46 shows the curve of the blood decimal in the case of M. B., age 18, suffering from chlorosis. On February 17, the blood decimal being only ·3, she was put on pulv. ferri carb., gr. x. ter., and the curve shows the rise of the decimal to ·5 on March 10, and its

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further rise to ·6 on March 14, after the iron had been left off. On the 14th half a pint of beef tea three times a day was added to her diet, and this beef tea was found on estimation to contain about 8·6 grains of uric acid to the pint, and I may say that it seemed to be very strong and good beef tea; she would then take about 13 grains of uric acid, or xanthin, a day.

On March 18 the blood decimal has fallen to ·54, and on the 22nd, when the beef tea was left off, to ·52.

I may point out, in passing, that uric acid given by the mouth to those who, like anæmic girls, have rather low nutrition, is more likely to remain in solution in the blood, because their blood is probably more alkaline than that of better-nourished individuals;

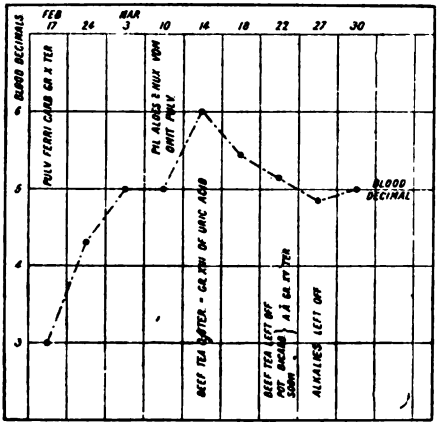

FIG. 46.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF IRON, BEEF TEA, AND ALKALIES.

therefore, the effect of giving uric acid is likely to be more marked in poorly-nourished individuals than in those who are robust and well fed, and dose for dose the effect on the blood curve will be greater in the former than in the latter.

Though I stopped the beef tea on the 22nd, I gave the bicarbonates of potash and soda, 15 grs. of each, three times a day, with the object of increasing the urate in the blood, and we see on the 27th that the blood decimal has further fallen to ·48. The alkalies were then left off, and on the 30th the blood decimal had risen slightly to ·5.

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I have no doubt that the whole of this fall was due to the uric acid taken, for the general tendency is for the blood curve to rise slowly for a considerable time after the iron is left off.

Fig. 47 is the blood curve of E. E., age 23, also suffering from chlorosis. On May 4, her decimal being at ·35, she was put on pulv. ferri. carb. as in the previous case. On May 26, the decimal having risen to ·56 the iron was left off. On June 2, when the decimal had risen to ·57, she was given beef tea = 13 grs. uric acid per day, and this was continued till the 8th, the blood decimal falling on the 5th to ·54, and on the 8th to ·53.

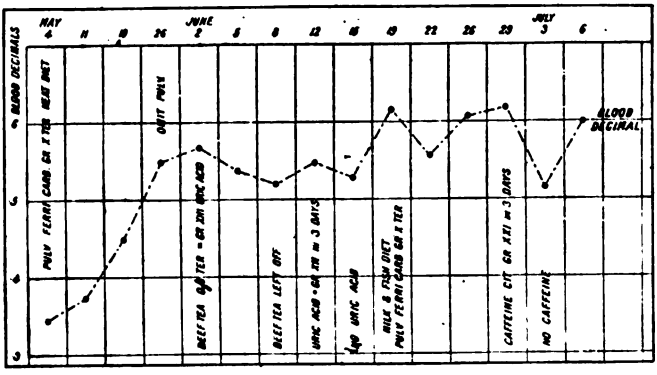

FIG. 47.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF IRON, BEEF TEA, AND CAFFEINE.

On the 12th, four days after the last dose of uric acid, the blood decimal had risen again to ·55. On this day, the 12th, she was put on the equivalent of 6 grs. uric acid for one day, and 3 grains each for the two following days, to try the effect of smaller doses, and on the 15th the blood decimal had fallen again to ·53, so that the effects of a small dose were fairly marked, and I think that a small dose will, perhaps, get uric acid into the blood more quickly than a large one, for uric acid, as I have said, interferes with its own solubility, and the salts contained in beef tea will in a similar way tend to depress the alkalinity of the blood, and cause the uric acid to be stored in the fibrous tissues and viscera instead of remaining in solution in the blood: and in producing changes in the blood decimal, we have not only to get it into the blood, but

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to keep it there so long as the kidneys will allow it to remain unexcreted.

On the 19th there is a remarkable rise of the blood decimal to ·62, making it look as though it would have gone on rising all the way from June 2, but for the uric acid taken.

On the 19th, iron was again given in the same dose as before, and it was rather a surprise, therefore, to find that on the 22nd, the blood curve had fallen to ·57, but I had forgotten the fact that, on the 19th, the patient was not only put on iron, but also on a milk and fish diet, having previously been on meat, and the change of diet no doubt produced a fall of acidity, acting like the alkali given in the previous case; this brought some of the previously stored uric acid through the blood, and the uric acid overcame the iron, and produced a fall in place of a rise in the blood decimal.

A similar explanation can be given of a point in fig. 46 which I omitted to mention. In this figure it will be seen that on March 10, the blood decimal failed to rise, though the iron was still being taken, and this, I think, was the result of some abdominal pain and digestive disturbance which was unfortunately produced by some aloes pills given her for constipation; the digestive disturbance no doubt produced collæmia, and the uric acid, as in the other case, overcame the iron so far as to prevent a rise of the blood decimal.

By the 26th, however (fig. 47), most of the uric acid has passed through the blood and been excreted, the iron then comes into action, and the blood decimal rises to ·61. On the 26th, the iron is left off, but the decimal again rises on the 29th to ·62.

On the 29th, citrate of caffeine was given, 9 grs. on the first day, and 6 grs. on each of two subsequent days. Now caffeine may for all practical purposes be regarded as uric acid, and my experiments on myself (fig. 28) show that, like uric acid, it first raises the acidity and clears uric acid out of the blood, causing freedom of capillaries and a diuresis; later, when the acidity falls, an excess of uric acid, proportional to the caffeine taken passes through the blood and into the urine;[1] and we see from the curve that caffeine brought down the blood decimal, just as uric acid does, for on July 3, we have a marked fall to ·52, which is followed by a rise to ·6 on the 6th, the drug having been left off.

[1] See also Prof. See, *Lancet*, 1890, i., p. 677.

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Fig. 48 shows the blood decimal of J. K., suffering from chlorosis. From April 11 to May 8 she was on iron, and we see the rise it produced in the decimal. On May 11 iron was left off, and on May 15 the blood decimal was the same as on the 8th. On May 15 and two following days the equivalent of 4 grains of uric acid were given, on May 18 the blood decimal had fallen, but it rose again on the 22nd and 25th, after the uric acid had been left off. However, on the 17th and 18th, menstruation was present, and, as this might have caused a fall of the blood decimal, I repeated the dose of uric acid on the 25th and two following days, and on the 29th the decimal had again fallen, to rise again on June 1 after the uric acid had been left off.

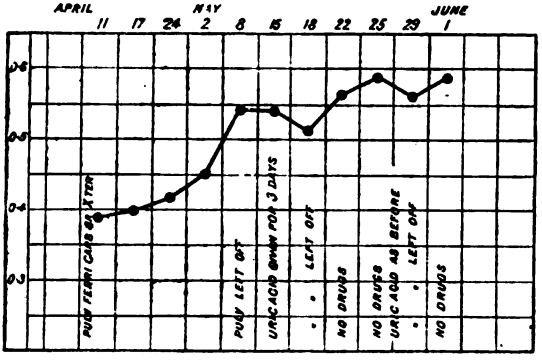

FIG. 48.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF URIC ACID.

There seems, then, to be very little doubt that the administration of uric acid and its passage through the blood (for a similar adminstration to myself does cause it to pass in excess through the blood into the urine, figs. 23 to 28) causes a distinct fall of the blood decimal in spite of the presence of a considerable amount of iron in the body. But iron does not always succeed so well as it did in this case, and then, as we shall see in the following case, it fails because it is unable to clear the blood of uric acid, for other drugs which have more power in clearing the blood of uric acid succeed. Fig. 49 shows the blood decimal of A. P., age 17, suffering from chlorosis, and below this for comparison I have placed the curve of the urine excretion in ounces.

I may say that she had been attending as an out-patient for more than three months, and taking iron the whole time, but on

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February 27 there was no improvement; the gums were very pale, and the face puffy and wax-like.

I took her in, examined the blood, and found the decimal at 0·34. I put her on pulv. ferri carb., and on March 6 the blood decimal was just the same; so that a week on iron and in bed produced no improvement. She suffered considerably from headache and dyspepsia, and I have little doubt that the dyspepsia kept the acidity low, and so prevented the iron from clearing the blood of uric acid, and hence, though given steadily for three and a-half months, it had practically done no good.

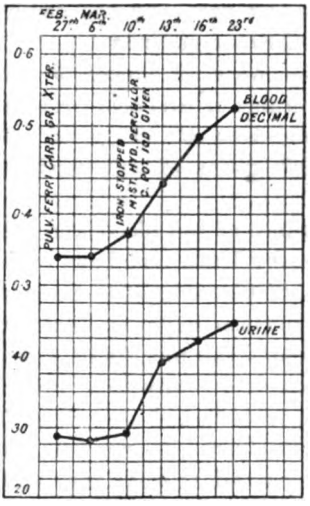

FIG. 49.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF IODIDE OF MERCURY.

To test this point I began to examine the urine, and on March 8 there were 29 ounces containing 267 grains of urea and 15·2 grains of uric acid, a relation of uric acid to urea of 1—17. On March 9 there were 28 ounces of urine containing 206 grains of urea and 13 grains of uric acid, relation 1—15.

Here then, while the patient was on iron we have evidence of a great excess of uric acid in the urine, and no doubt also in the blood, which explained her headache and scanty urine (for the urinary water is, as we have seen, in everyone inversely as the uric acid excreted along with it) and her œdematous, almost myxœdematous face, from retention of fluids in her tissues, and

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also completely explained why the iron had for so long failed to do good.

On March 10, however, there was a slight improvement, and the blood decimal had risen to 0·37, but as I had found such an excess of uric acid in the urine in spite of the iron, I decided to stop it and give a drug which I knew had more power of clearing uric acid out of the blood and urine. I accordingly put her on the ordinary mist. hydrarg. perchlor. c. pot. iod., three times a day, and the rest of the figure shows its effect on the blood and urine.

On March 13 there were 39 ounces of urine, containing 304 grains of urea, and 10·8 grains of uric acid—relation 1—28. Note the increase of water and urea and the decrease of uric acid in illustration of the law above mentioned.

On March 16 there were 42 ounces of urine, containing 232 grains of urea and 9·1 grains of uric acid—relation 1—25.

On March 23 there were 45 ounces of urine, containing 332 grains of urea and 9·7 grains of uric acid—relation—1—34, or normal.

And with this clearance of the blood and urine of uric acid the blood decimal went up by leaps and bounds, and having risen in eleven days on iron only 0·03, it rose 0·06 in three days on iodide of mercury, and 0·15 in thirteen days, reaching 0·53 on March 23, a height which more than three months on iron had quite failed to raise it to; and we now know why this was so, for the one drug cleared the blood of uric acid, and the other failed to effect this result. I know, however, from experience in other cases that even the iodide of mercury may fail to clear the blood and urine of uric acid, and then, like iron in the above case, it also fails to produce any continuous improvement in the blood decimal.

The marked rise in urinary water, which coincided in this case as it always does with the equally marked fall in uric acid, soon removed the excess of water from the tissues, and her face assumed a natural appearance, her appetite and digestion improved, and she considered herself cured.

In this case I have very little doubt that but for the dyspepsia the iron would have been able to clear out the uric acid at first, and then she would have been cured in six or eight weeks instead of remaining almost unaffected at the end of three months. Now it is well known that Murchison and others have pointed out that in some cases iron will not cure anæmia till the liver has been got into proper order, and the drug he used to get the liver into order was mercury (see Murchison, "Croonian Lectures," *Lancet*, 1874, vol.

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i., p. 504, and fig. 17, chapter iii.) We can now see that this mercury did good, not by any special action on the liver as was supposed, but because it cleared the blood of uric acid, and so altered at once the circulation and nutrition of the whole body; and any other drug that clears the blood and urine of uric acid produces the same fall in excretion of uric acid and rise in excretion of urea, but some have more power, and will succeed in clearing the blood of uric acid when others have failed.

I was much interested to hear Dr. Dundas Grant say at a recent meeting of the Hunterian Society (*Lancet*, 1897, vol. i., p. 1275), that chloride of ammonium is not only useful in headache, but is in his experience a hæmatinic, and had been recommended as such by Dr. Barnes and others, for there is no doubt in my mind that we have here one more substance which clears the blood of uric acid, and improves its condition by doing so; here also is the explanation of the relief it affords in headache, neuralgia, and hepatic congestion. I have already pointed out with reference to sp. ammon. aromat., that ammonium salts raise the acidity of the urine, and I shall have to point out later that they do harm in acute rheumatism; and in the chloride we have not only the ammonium, but a powerful mineral acid is also introduced into the body.

Chloride of ammonium is also a well-known precipitant of uric acid outside the body, and as we shall see further on it may be possible by means of the microscope to watch its effects on the uric acid and xanthins in the blood itself.

On the other hand, we now know that you have only to introduce into the body and blood an excess of uric acid to quickly undo all the good that iron, mercury, salicylates, or anything else has done, which still further emphasises the fact that they do good merely by clearing the blood of uric acid; and if you give uric acid along with iron the blood decimal falls, or at least fails to rise any further, so long as the uric acid is continued, which parallels what we have just seen in Nature, that when there is a great excess of uric acid in the urine and blood, iron may be administered for months without effect.

In the *Lancet*, 1895, vol. i., p. 769, it is said that sulphate of copper is far better than iron for the treatment of anæmia, and the dose recommended is $\frac{1}{3}$ to 1 grain twice a day; this dose is much smaller than that of iron, but much larger than that of mercury in the mixture given in fig. 49, but, like iron and mercury, copper is well known to form an insoluble compound with uric acid.

I may say at once that these and other similar experiences, have

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left no doubt in my mind that just as iron runs up the blood decimal, uric acid brings it down; and that when the one is acting in opposition to the other, the uric acid is the more powerful.

But as soon as the blood is cleared of uric acid, the general metabolism, being freed from the incubus of obstructed capillaries, goes ahead, there is a general rise of urea and acidity, which keeps the blood more or less clear of uric acid, and iron is then able to act and bring about permanent improvement.

I have every confidence that I can in this way do anything I like with the blood decimal, and that anyone who will take the trouble to repeat my experiments will get similar results.

In addition to the figures given above, I have examined my own blood and urine side by side every day for many weeks, and find

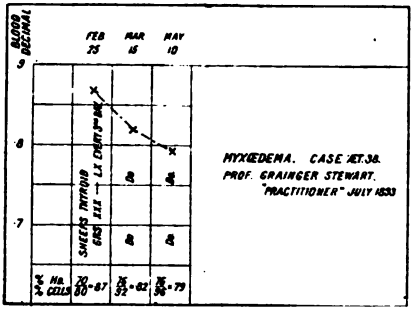

FIG. 50.—CURVE OF BLOOD DECIMAL IN MYXŒDEMA SHOWING THE EFFECT OF THYROID FEEDING.

that the changes are practically constant, and that with every marked rise of uric acid excretion the blood decimal falls, and *vice versa;* and indeed I would undertake to tell correctly, from a daily examination of the blood of a patient, whether the uric acid had risen or fallen each day, the urine being examined by someone else.

To conclude this part of the subject, I will just show a small figure, No. 50, which proves that others have obtained results which are practically identical with my own, without knowing how they were produced.

In my paper in the *Journal of Physiology*, vol. xv., I suggested that extracts of thyroids and other glands possibly owe no small part of their activity in myxœdema and skin diseases to the stimulant

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properties of the uric acid and other nitrogenous extractives in which they are known to be rich; and I can prove that in myself the taking of thyroid glands or a thyroid extract produces results which are identical with those produced by so much uric acid (see fig. 29); that is to say, there is a first stage of stimulation with rising acidity, well being, free capillaries and diuresis (just as with caffeine also), followed later, when they are left off, by falling acidity with plus excretion of uric acid, obstructed capillaries and scanty urine, and with these latter a fall in the blood decimal, just as with uric acid taken in any other form.

It is interesting to note in this connection that myxœdema, like asthma, Raynaud's disease, and dropsy, is better during pregnancy, or during fever, and we shall have an instance of the effects of the fever of measles on the dropsy of Bright's disease in chapter xiii. Again, myxœdema, like certain skin diseases, may be worse at the menstrual periods, while arthritic troubles, which stand at the opposite pole of causation, tend to be worse during fever and may be better during menstruation (see *Lancet*, 1893, vol. ii., p. 744; *British Medical Journal* Epitome, September, 1892, p. 43, and *Ibid.*, February, 1892, p. 25.)

I was, therefore, much interested to see in the *Practitioner*, July, 1893, a paper by Prof. Sir T. Grainger Stewart, in which he gives the blood factors in a patient who was being fed with 30 to 60 grs. of thyroid gland every third day for myxœdema.

Fig. 50 shows the blood decimal curve constructed from the figures which he gives, and demonstrates that this feeding with thyroids produced a steady fall of the blood decimal. It is true that the red cells rose from 80 to 96 per cent., but this is simply due to the concentration of the blood; for thyroid gland, as I have said, just like uric acid and caffeine causes diuresis (see fig. 29); the hæmoglobin, however, did not rise proportionately, and on the last occasion it did not even rise absolutely, and so the result is a steady fall of the blood decimal, doubtless due, as in my own curves, to an excess of uric acid passing through the blood.

Professor Stewart's patient it is interesting to note also, suffered very markedly with all the symptoms of an excess of uric acid in the blood; such as weakness and general soreness, with tightness and oppression in the chest, passing later into severe dyspnœa, with blood-stained expectoration; her asthmatic trouble being complicated by the presence of old disease of the mitral valve (see chapter ix.)

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It is now easy to understand the causation of chlorosis and anæmia, and their relation to dyspepsia and bilious attacks, for these disturbances cause excess of uric acid to pass through the blood; but there are other most interesting relations between the development of girls and the causation of these troubles, which furnish at least some explanation of the frequency with which anæmia is met with in young women.

As to the way in which uric acid produces these blood changes it is not easy to say anything definite; but we have seen that it obstructs the capillaries throughout the body and in this way diminishes the formation of urea and the production of animal heat, and we shall see in the next chapter that the fall of urea it produces is contemporaneous with the presence in the blood and urine of an ill-metabolised and diffusible albumen, and that when we give drugs which clear the blood of uric acid, the urea increases just in proportion as the diffusible albumen diminishes. In a word, the urea which does not appear in the urine is accurately represented by the diffusible albumen which does, and by altering the amount of uric acid in the blood, and so controlling circulation, metabolism and combustion, we can make the one give place to the other.

It is clear then that uric acid controls the results of many metabolic processes, and determines the properties of some constituents of the blood; and we have only to extend this power to the corpuscles to understand the phenomena both of paroxysmal hæmoglobinuria, and anæmia; they and all their relatives are results of defective metabolism, which again, just as in the case of fatigue, is the result of defective circulation.

And now as to the causation of chlorosis. It will, no doubt, be readily admitted that we meet with it chiefly in women between the ages of 16 and 25. How do girls and women of these ages differ from boys and men of the same ages? As you know well, a girl at about the 13th year develops with enormous rapidity, and her weight may increase by as much as 11 lbs. in this one year, as she dashes at a bound from childhood into womanhood.

Now, this very rapid growth and development entails a corresponding rapidity of tissue change and metabolism, with a very large formation of uric acid and urea per pound of body weight—this being always much greater in the child than in the adult. But high urea formation is always accompanied by high acidity, that is to say, the urine will be highly acid and the blood lowly alkaline. The blood alkalinity being low, it will be but a bad solvent of uric

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acid, and hence a considerable proportion of the large amount of urate formed in these years of active metabolism will not be held in solution in the blood and excreted, but will be retained and deposited in various parts of the body, giving local signs of which we shall speak presently.

Unfortunately, later on a girl's metabolism falls very greatly, and by the end of the 18th year her increase in weight is almost *nil;* with this there is a great fall in the formation of urea and of acids, and the blood becomes more alkaline; as a result of this it becomes also a better solvent of uric acid, and it now takes up and passes into the urine so much uric acid—probably several hundred grains—as was stored in the tissues during the preceding period of active metabolism, from 12 to 14. Hence, from 16 to 19, or later, she will have an excess of uric acid passing through her blood, and will suffer from its effects on the blood decimal—namely, chlorosis.

To illustrate this point a little further, I give in fig. 51 a curve showing the annual increase in weight of boys and girls.[1] From this we see that the greatest development in girls is in the 13th year, and in boys not till the 16th; and though the boys' curve falls very greatly in the 17th and 18th years, they are still increasing about 5 lbs. a year when the curve ends.

Now I think that girls in their more early development will probably form more uric acid and urea per pound than boys in their later development, and when later on the girls' increase is almost *nil*, the uric acid previously retained will pass through the blood both in greater quantity and more suddenly than it does in boys, whose increase is for several years later very considerable and their acidity not so low. I have therefore added to Dr. Stephenson's curves a line representing the probable effects of the girls' increase in weight on the formation of urea and acids, and a broken line below showing the effect of this on the excretion of uric acid, and from these we see at a glance that the chlorosis and anæmia of 18 are the result of the passage of an excess of uric acid through the blood, which again is the result of a previous storage of this substance from 12 to 15. Add to this that just at the time when a girl's increase of weight is coming down, and her urea and acidity falling, menstruation is established; and that even if this does not upset digestion and appetite, it often obliges girls to keep quiet for several days, so that its result is to still further reduce urea and acidity, and still more markedly flood the blood

[1] Copied from a paper by Dr. W. Stephenson, *Lancet*, September, 1888.

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with uric acid, thus completely accounting for the increase of her chlorosis, and the functional troubles so often met with at menstrual periods.

I notice that a recent observer (Dr. Luff, *Lancet*, 1897, vol. i. p. 946) thinks that there is no uric acid in the blood of men and

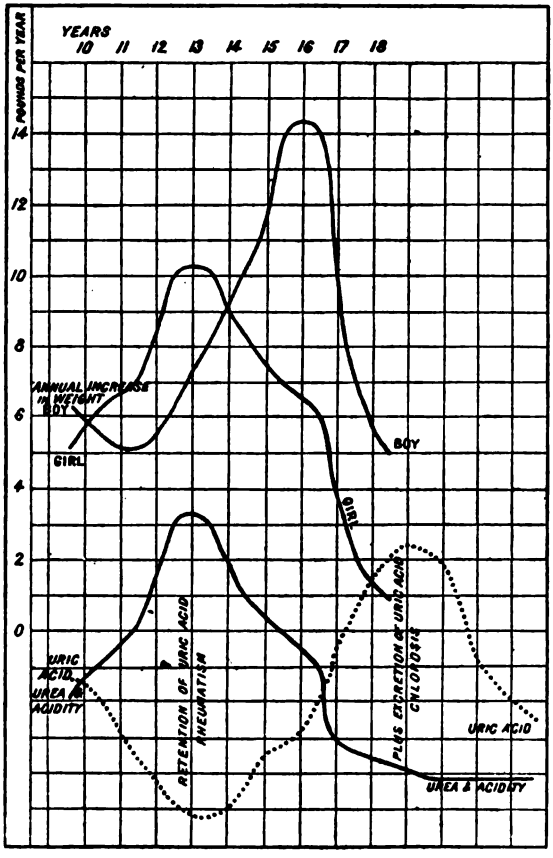

FIG. 51.—CURVES SHOWING DEVELOPMENT IN BOYS AND GIRLS AND ITS EFFECT ON THE EXCRETION OF URIC ACID.

animals in health, and I have already quoted Prof. von Jaksch's observations showing that he found none in a few cases; but Sir A. Garrod, it may be remembered, did find some in healthy blood ("Gout and Rheumatic Gout," ed. iii., p. 113).

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I differ from some of these observers, merely in thinking that a small quantity is very often present in the blood of man even in perfect health, and that there is more at some hours of the day and less at others, as shown by the changes in the blood itself and the corresponding changes in the excretion in the urine (see fig. 45), and, indeed, the results just shown in the previous figures are absolutely inexplicable, if an excess of uric acid in the urine does not mean a corresponding excess of uric acid or of xanthin in the blood.

The blood changes can, as we have seen, be produced by swallowing either uric acid or xanthin, which are chemically so closely related (see Lea, "Chemical Basis of the Animal Body," p. 174), but the conditions which control the excretion of this substance in the urine correspond, at numerous points, with the known solubilities of uric acid, and not with that of some of the xanthins; and as I have already pointed out in chapter i., eating of meat has been found by very numerous observers to increase the excretion of uric acid in the urine, while the xanthins are present in that fluid only as mere traces, and yet meat, like tea, coffee and cocoa, introduces into the body probably nothing but xanthin, which is, therefore, we must conclude, converted into uric acid.

Again, I agree with all these observers in finding some uric acid in the blood in disease; and not only so, but my observations are in complete accord with those of Prof. von Jaksch and Sir A. Garrod, as I have found most in the blood in exactly the same conditions as they have found most, and have shown that the quantity rises and falls in these conditions in exact accordance with the factors affecting its solubility, which are practically identical both for physiology and pathology. Then again, in several pathological conditions, as leucocythæmia on the one hand and acute rheumatism on the other, the quantity in the urine is well known to correspond with that in the blood; and if this holds in pathology it is difficult to see any reason why it should not also hold in a minor degree in physiology.

The condition of the blood itself also varies in pathological conditions just as in physiological or artificial ones, with the quantity of uric acid in the blood and urine (see figs. 49 and 65.)

Dr. Luff, I believe, does not tell us in how many cases he examined the blood, nor does he tell us what, from my point of view, is still more important, the hour at which it was drawn, as I should only expect to find it in quantities that could be identified in any blood that could reasonably be drawn from a living man at some hours of the day; and even at alkaline tide hours, accidental varia-

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tions, as shown, for instance, in fig. 45, might cause it to appear to be absent, so that a large number of results carefully published, with full details as to time of day, food, exercise, drugs, and conditions of the subject, would have to be produced to prove absence of uric acid from normal blood. And even then it would be necessary to give some other explanation of my physiological and pathological results, which can be reproduced to any extent.

It seems also to be quite unnecessary to postulate, as Dr. Luff does (*Lancet*, 1897, vol. i., p. 944), an altered condition of the renal epithelium to account for the accumulation of uric acid in gout, when the excretion of this substance varies from hour to hour with the acidity of the urine, and can be made to vary to almost any extent by administration of acids and alkalies; and why, if this substance does not come from the blood, does the blood show corresponding changes?

Again, as we shall see in the following chapters, an extremely diseased kidney may yet excrete a great excess of uric acid, and we have already seen that a perfectly normal kidney may, in conditions of low alkalinity of the blood, excrete very little.

As regards the presence of uric acid in the blood, I think that a recent observation of Mr. Barker Smith is of some interest, and may eventually lead to valuable results.

Now, this observer pointed out (*Medical Times and Hospital Gazette*, September, 1896), that using chloride of ammonium as a precipitant he was able to obtain microscopic evidence of the presence of uric acid or urates in urine diluted so as to contain about one per forty thousand of these substances, and this led him to examine the blood for similar microscopic evidence of urates, and he points out that he apparently got positive results.

The following are the directions he gives:—"Prick the finger with a needle and obtain a droplet of blood, touch it with the cover glass, then with the needle add a minute portion of carbonate of soda solution, and then a similar portion of solution of sal ammoniac. Mix together and examine under a fourth or fifth object glass after half-an-hour."

The solutions used appear to be sodii carb., 10 per cent., and ammon. chlor., 20 per cent.

He further says, "Granular urates may be seen distinct from micrococci and from albocytes; some appear in the blood corpuscles."

In some subsequent writings on these points he acknowledges that the granular urates have to be distinguished from granules

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thrown down by the solutions used, as well as from micrococci and albocytes.

Thinking over this matter it soon occurred to me that having as I believe almost absolute power over the quantities of uric acid in the urine and also in the blood, it would not be very difficult to put these statements to such tests as would very promptly settle the question of their value one way or the other.

What I had to distinguish these possible urates from were (1) micrococci, (2) albocytes, and (3) granules from the solutions used.

With regard to the latter it appears probable that by using as far as possible constant and small quantities of the solutions, they may be averaged and neglected, and as regards albocytes and micrococci there is no reason to suppose that they will vary constantly with the uric acid present, and if the granules are found to vary constantly with the amount of uric acid in the urine in health, and what is known of its presence in the blood in disease, we may similarly neglect albocytes and micrococci.

Now, as we know uric acid is present in the urine in large amounts during certain hours of the day, and in very small amount during certain hours of the evening and night, and it can be made to vary in the urine at any time by very numerous drugs, and I have given my reasons for believing that every such artificial or natural variation in the excretion in the urine is the index of a similar variation in the quantity present in the blood.

Now, if this is true, and if the granules pointed out under the microscope by Mr. Barker Smith are urates, or xanthins (for xanthin also appears to be precipitated by chloride of ammonium) they ought to vary in quantity with the normal urinary excretion of uric acid in physiological conditions, with the artificial alterations in excretion produced by drugs or feeding with uric acid or xanthins and with the best known and attested pathological variations in the amounts of uric acid in the urine and blood.

I accordingly began to examine my own blood night and morning, taking it in the morning at some hour between 6 a.m. and 9 a.m., when uric acid is above urea, and comparing this with 10.30 or 11 p.m., when uric acid is below urea (fig. 3). And I soon found that there were always many more of these granules present in the morning hours than in the evening hours. Thus, in the morning it was no uncommon thing to find granules present in the relation of one to every three, five, or eight red cells, while in the evening the relation was one to ten or fifteen, or more.

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Then one morning, when I had all the signs of collæmia and high blood pressure after a late and rather indigestible supper the previous night, I examined the blood, and finding more granules than usual, I took a dose of calomel and watched the urine half hour by half hour and when a diuresis came (the urine rising from about 35-40 cc. in an hour up to 70 cc. in the same time) I examined the blood again and found a much smaller number of granules.

And it seems to me very unlikely that either albocytes or micrococci could present such constant variations with the time of day, and as to granules from the solutions, they were used in the same way each time, and it is hardly likely that they could account for such constant variations. Besides any natural blood elements would be more numerous after a diuresis than before it, but it was just the reverse with these granules.

I then began to examine into the possibilities of Pathology and I put the matter here to the most severe test I could devise.

For I think there is no fact more generally agreed upon by workers on uric acid than this, that if you are ever likely to find excess of uric acid in any blood, it is in that of a patient who suffers from chronic gout, more especially if it is conjoined with chronic Bright's disease, and I happened to have such a case under my care; and I think it would be further agreed that if you wish to find a blood almost completely free from uric acid you had better examine that of a patient suffering from acute fever, as both Sir A. Garrod and Professor v. Jaksch have pointed out that uric acid is absent from the blood under these conditions.

I accordingly took the blood of a patient suffering from acute pulmonary disease with a temperature above 102° F., and I prepared for comparison with it a similar specimen of blood from my case of chronic gout and chronic Bright's disease.

And the result was absolutely conclusive, a single glance down the microscope sufficed to tell which was which, for the blood of the febrile patient contained very few granules less than my own blood usually contains; while that of the gouty patient contained an enormous number, three or four times as many as I had ever seen in my own blood; and I believe the relation of granules to blood cells in this gouty blood was practically one to one; and I repeated my examination several times and always found more in this patient's blood than in any I have examined.

The fact that the febrile blood did contain some granules may be taken to show that there are some granules in all such mixtures

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of blood and salt solutions, even apart from urates, and the difference between the number of granules in the febrile blood and the chronic gout blood may be taken to represent the largest number of granules likely to be met with in any blood as the result of excess of uric acid and xanthin.

I then produced an artificial increase of the uric acid and xanthin in my blood by swallowing some small quantities of Theobromine, and again the granules seemed to increase or diminish with the uric acid found in the urine.

Thus, one day when the uric acid urea relation in the urine was one to twenty-six and when 3½ grs. of uric acid passed through the blood, I examined it at 4.50 p.m. when there was some fairly marked mental depression, and found granules in the relation to red cells of one to four; and on this afternoon my blood could not at once be told from that of the gouty man above mentioned, and it was only on carefully counting with a micrometer eye-piece that his blood was found to give a relation one to three or even one to two.

On the following day at the same hour I again examined my blood, there being no mental depression and the uric acid urea relation in the urine of the day being one to thirty-six, and in this blood I found relations of one to sixteen and one to eighteen, and this blood could as on other occasions have been easily distinguished from that of the gouty man.

It is my intention to continue this investigation and to repeat and vary these experiments many times, for so far as I have gone it certainly seems as if some of these granules must be urates or xanthins; and the test is so simple and easy to perform, that I am in hopes that many will take it up, and we shall then soon learn its real value and how far it may be depended upon.

Then, again, if we look at this figure (51) we shall see that we have got not only a complete explanation of the causation of chlorosis, but that we have also unexpectedly come upon an equally complete explanation of the girl's great tendency to rheumatism, as compared with her brothers; for I have for years been pointing out[1] that what we call gout or rheumatism is really the irritation of certain joint structures by uric acid or urates retained in those structures; and that they are retained in those structures by the same causes that prevent their excretion, and bring about their retention in the body in general, namely, a rise

[1] *Practitioner*, February, March, and April, 1891, and *British Medical Journal*, July, 1888.

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of acidity, or the presence in the blood of any substance whose urate is insoluble.

Now the retention in this instance is produced by a rise of acidity, and the joints are one of the places in which the urate is detained; it is little wonder, then, that girls are specially liable at this period of their lives to acute rheumatism, and Dr. Cheadle says[1] that girls of 10 to 15 years old are twice as liable to rheumatic fever as boys of the same age; these years including I remark, the period of their most active metabolism.

But we already know that migraine and rheumatism alternate, and we have recorded on p. 369 a quotation from Dr. Liveing which says that a woman became subject to megrim *after puberty*; now fig. 51 tells us exactly why her trouble came at that time as well as why epilepsy and chlorosis tend to originate at the same period of life.

Probably boys are liable to rheumatic fever from a similar cause at 16 years of age, but their active metabolism coming when they are older, they probably form less uric acid per pound than girls; and, further, they probably retain much less uric acid at this time owing to their more active habits of life.

For it follows from our first principles of urate excretion, that other things being equal, those in any given period of life retain most uric acid in their body who take least exercise, and those retain least uric acid in their body who take most exercise, which explains Cullen's well-known observation that gout seldom attacks those employed in constant bodily labour (see figs. 39 and 40.)

Now no one, I suppose, will deny that boys take much more exercise than girls all through school life, and especially as compared with girls at and after the commencement of menstruation. We see, then, that boys differ from girls in that their active metabolism comes later, when their formation of uric acid per pound is probably smaller, and that owing to their greater bodily activity, they probably retain a smaller amount of the uric acid they form; while, lastly, their activity and nutrition are better continued and maintained, and are not subjected to the depressing effects of menstruation, so that any urates they have retained pass more gradually through their blood; hence they escape the chlorosis and anæmia from which their sisters suffer.

Paroxysmal hæmoglobinuria represents, I have no doubt, a

[1] *Lancet*, vol. i., 1889.

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similar but more acute fluctuation in the excretion of urates, probably often related to dyspepsia and gastric upset in exactly the same way that migraine, epilepsy and Raynaud's disease, are related to it, and it is paroxysmal just as they are paroxysmal, in relation to the fluctuations in urate excretion.

Anæmia associated with enlarged spleen is doubtless related to the large quantities of uric acid met with in the blood and urine of these cases (see pp. 367 and 384.)

The way in which the excess of uric acid in the blood is brought about I have already gone into; and as I have said above, the increase of white cells met with in these cases may be entirely secondary.

In the *Practitioner*, August, 1890, Dr. F. W. Mott wrote an interesting paper on the spleen as a centre of destruction of red blood cells, and it may be noted in this connection that Dr. Hunter (*Lancet*, 1892, vol. ii., p. 1,318) points out that certain substances (toluylendiamine) which have a destructive action on the blood act far less powerfully after the spleen has been removed; and no doubt if uric acid destroys the blood elements, they are certain to meet it in concentrated solution in the spleen, and the facts just mentioned suggest strongly that the action of toluylendiamine is indirect.

The effects of fevers in producing anæmia are easy to understand, for they diminish the alkalinity of the blood and lead to a storage of urate in the body, and this, when the fever ends, finds its way back into the blood (see facts about pneumonia, pp. 71 and 174), causing post-febrile uricacidæmia with post-febrile bradycardia, high tension pulse, depression of mind, and metabolism and subnormal temperature, an identical sequence of events with those producing chlorosis. The excess of uric acid met with in the blood and urine after malaria and other fevers, with or without enlarged spleen, is thus, I believe, the result of the storage of urate that took place during the fever (compare also previous remarks on rheumatism in girls).

In vol. lxxv. of the *Transactions of the Royal Medical and Chirurgical Society*, Dr. A. E. Garrod has an interesting paper on the anæmia of rheumatism, and the relation of the blood changes to the excretion of uro-hæmatoporphyrin.

In several of his curves, "worth," which corresponds with my blood decimal, remains steady or rises during the fever, and falls afterwards as the temperature becomes subnormal, that is to say, during the fever the urate is all in the joints, and there is none in

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the blood except in combination with salicylates (see previous remarks on the action of salicylates in anæmia); as the fever passes off there is post-febrile uricacidæmia with a fall of the blood decimal, just as we should expect when urates combined with alkali are passing through the blood; and in at least one of Dr. Garrod's cases, the "worth" fell at the end of the fever *in spite* of iron being given (see also Dr. Garrod's remarks, previous reference p. 191).

He also notices a corresponding increase of white corpuscles, just as in the similar condition I have mentioned above, and as observed by Dr. Wheaton. I should expect a fall of the blood decimal just before the onset of the fever, when according to my explanation of the causation of acute rheumatism, there is sure to be an excess of uric acid in the blood (see chapter xvi.), but Dr. Garrod's statements are not very definite with regard to this point.

The effect of all fevers on the blood decimal is probably the same as that of acute rheumatism, and I found in a case of pneumonia, that at the time of the post-febrile uricacidæmia with subnormal temperature the blood decimal was ·55, while a few days later, when the temperature had again gone up to normal, it had risen to ·60.

It is, again, quite easy to explain the effects of hot weather and of tropical climates in producing anæmia, for heat increases the alkalinity of the blood and the urate it will hold in solution; and this will have most effect in those who eat meat, and so introduce much urate into their body; and least in those who live on vegetables and fruits, and so ingest but little uric acid (see chapter xvii.)

The effects of diet also are well known and easily explained, for Dr. Mackenzie points out that meat diet increases the destruction of red cells (*Lancet* or *British Medical Journal*, 1891, vol. i.), and others have pointed out that farinaceous diet does good, and that pale, anæmic children are most common among the "well fed" upper classes (*British Medical Journal*, 1890, vol. ii., p. 85) —in my opinion, "not wisely but too well" fed upper classes.

The paper which immediately precedes mine on anæmia in the *British Medical Journal*, 1893, vol. ii., p. 670, is one with the heading "Preliminary Report on the Causes of Chlorosis," by E. Lloyd Jones, M.D., and this contains so many points of interest, and so many which, I think, the causation by uric acid will be found to give a complete explanation of, that I may as well mention some of them here.

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Thus, Dr. Jones points out that after fifteen years of age the specific gravity of the blood falls in the female while it continues to rise in the male, and that this is the age at which girls become anæmic.

But if this anæmia and chlorosis is, as I am suggesting, the result of excess of uric acid in the blood, the causation of which at this time of life I have already gone into, it is not difficult to see that this collæmia almost entails a fall in the specific gravity of the blood, because it prevents the outflow of water from it by any or all the glandular organs of the body.

It is easy for anyone to convince themselves in two or three hours' work that this is a fact; let them produce in any of the ways previously described so much collæmia as shall markedly diminish the excretion of water in the urine, and watch the blood meanwhile; they will find that hour by hour as the urinary water diminishes the water in the blood increases; that is to say, there is a relative diminution of both cells and hæmoglobin in the given quantity; conversely, when they clear uric acid out of the blood and produce a diuresis, they will find that the relative quantities of cells and hæmoglobin rapidly return to the position they held before the experiment began.

In my own case, and in the cases of anæmia I have investigated, I have come to believe that I can tell from the concentrated or hydræmic condition of the blood whether there has or has not been a diuresis produced by any drug given.

I look, therefore, upon the fall in specific gravity of the blood of the female which takes place at fifteen as the result of more or less collæmia, which produces in the ways sketched out above both hydræmia and anæmia, and this is itself the result of her very active metabolism at thirteen now coming to an end, and of her menstruation now establishing itself.

As the male is not exposed to these great fluctuations in metabolism with the collæmia they produce, he does not show any corresponding blood changes.

His metabolism goes more steadily ahead, and he lives also, be it observed, at this time of his existence, a much more healthy life than his sister.

I do not believe that there is any "natural tendency," either to a fall in the specific gravity of the blood or to chlorosis; they are simply the results of our meat-eating habits, and of our civilisation.

If our girls did not eat so much meat, they would not store so

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much urate in their time of active metabolism at thirteen, and if at fifteen they led the life of healthy active savages, instead of resting, lying up and becoming semi-invalids, there would be none of the present great fluctuations in their metabolism, but as in the case of their brothers, their development would go more steadily ahead, there would be no falling urea and acidity, no collæmia, and, consequently, no hydræmia and anæmia.

Further on, Dr. Jones seeks to establish a connection between chlorosis and disturbance of splanchnic innervation with dilatation of gastro-intestinal vessels, and he goes on to say, "This I conceived to be brought about in a reflex manner, and this appeared to me to be the more likely since I had met with some cases in which the usual gastro-intestinal disturbance, together with marked chlorosis, had rapidly followed a shock or chill—generally a shock or chill occurring about a menstrual period." Exactly so, and causing, therefore, a great fluctuation in the excretion of uric acid and the amount passing through the blood (see figs. 30 and 31).

Before leaving the subject of anæmia, it may be useful to give a short summary of the facts of the case.

First, then, by the clinical observation of paroxysmal hæmoglobinuria and Raynaud's disease, and of splenic leucocythæmia, chlorosis and anæmia, and the relation of many of these troubles to "bilious attacks," dyspepsia and menstruation, I was led to believe that there was an important connection between the blood changes and an excess of uric acid in the blood and urine. As to these facts, I am at one with other observers, but differ from them merely as to their meaning and causation.

Secondly, there is my observation that the value of my blood decimal appears to vary from day to day, even from hour to hour, with the amount of uric acid passing through it, and that if intentional variations are produced in the uric acid, the blood decimal follows suit.

I believe, also, that my blood will generally compare very favourably with that of other men of my own age who eat more animal food than I do.

Thirdly, there is my observation that the same holds good for others also, and especially for anæmic and chlorotic patients.

Lastly, we see that the knowledge thus acquired enables us to explain many of the chief points in the causation of these diseases, and will, doubtless, in the future enable us to explain still more.

Thus, I believe that many whose professional experience goes back 30 or 40 years would agree that chlorosis is much more

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common now than formerly, and hence I was interested in the remark of a woman among my out-patients at the Royal Hospital for Children and Women, Waterloo Road, who said with reference to her daughter's chlorosis, "Ah, sir, we never used to see this sort of thing when I was young." Now, if her observation is correct as to the facts, what has happened in the 30 or 40 years of her recollection. Why, agriculture has been ruined and the people driven more and more from the country into the towns, where they have aped the meat-eating habits of their social superiors, and increase of chlorosis is one of the results of this. But even in country towns they are now pale, as observed by me in a recent visit to Carlisle, but Carlisle has a public abattoir, of which it is proud, and curiously enough, the next object of interest on the list (B.M.A. membership card, 1896), is the human cemetery; humanity itself being the cemetery of the animals, as I believe, to its infinite hurt.

I have mentioned above, that one of the blood changes met with in paroxysmal hæmoglobinuria is an increase of coagulability; and several things seem to render it probable that if uric acid thus directly or indirectly increases the coagulability of the blood, it may exercise an important influence in the pathology of thrombosis.

The frequent clinical connection between thrombosis and gout or diabetes, of both of which I shall have something to say presently, is too well known to need more than mention; and a similar relation is often found between thrombosis and certain post-febrile and puerperal conditions; and after what I have already said about these, I need hardly insist on the fact that one point common to all these diseases is the frequent presence of considerable excess of uric acid in the blood; then again, unless my clinical observation deceives me, thrombosis is not very uncommon in Bright's disease, and in this disease (as we have seen in chapter iii.) the researches of Professor R. von Jaksch confirm my own in showing that an excess of uric acid is very frequently to be found in the blood (*Centralb. fur Inn. Med.*, May 23, 1896.)

In the *Lancet*, 1894, vol. i., p. 1446, is the record of a case of thrombosis following an attack of influenza, and said to be due to the breaking up of white blood cells. I think it is much more probable that it was due to the post-febrile collæmia which followed the influenza, and that the increase of white cells and the increase of coagulability were, just as in paroxysmal hæmoglobinuria, the results of the collæmia.

From this point of view also I was very greatly interested in

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Sir J. Fayrer's article on "Intra-vascular Coagulation and Pulmonary Thrombosis" (*British Medical Journal*, 1893, vol. ii., p. 165), for in many of the conditions which he mentions, such as malaria, splenic disease, puerperal conditions, hot, damp weather (see also causation of fatigue, figs. 39 and 40), and especially surgical operations in hot, damp weather, it seems to me that there is hardly room to doubt that a great excess of uric acid would often be present in the blood.

I shall mention in chapter xiv. the effects of surgical operations in increasing the excretion of uric acid and urea, and I have no doubt that, combined with hot weather, these would greatly increase the quantity of uric acid passing through the blood.

Then, again, I notice in the *Lancet*, 1896, vol. i., p. 475, a case of fatal pulmonary apoplexy in a girl of 14 years, which came suddenly after a walk just at the end of a perfectly normal monthly period; but here we have at least three causes of collæmia, the exercise, the menstruation, and the girl's age, referred to in fig. 51. Similarly, a case of pulmonary thrombosis recorded in the *British Medical Journal*, 1896, vol. ii., p. 1504, coming after enteric fever is said to be due to debility, but here again, I think, we must not forget post-febrile collæmia.

Lastly, if as I have suggested (p. 148), colloid uric acid mechanically obstructs the capillaries, and if from time to time small portions of this obstructing substance are carried past the capillaries into the veins, we can at once see how they may come to form nuclei of thrombosis, if the colloid is not dissolved, as the blood gets warmer in the deeper tissues.

So that this colloid mechanical theory may also help us to understand the observed connection between gout and thrombosis.

And once a coagulum has formed round such a nucleus, it will not dissolve even in the warmest parts of the central circulation, though the colloid uric acid alone may completely disappear there.

Lastly, there is another point among the symptoms of paroxysmal hæmoglobinuria, of which I am now, I believe, able to give a pretty complete explanation.

It will be readily admitted by other observers, that in the urine of paroxysmal hæmoglobinuria, oxalate crystals are very frequently present; let us enquire further as to their meaning.

In the *British Medical Journal*, 1885, vol. i., p. 167, Dr. Lauder Brunton points out that it has been shown that when sulphuretted hydrogen is allowed to act on a concentrated solution of urates,

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oxalate of lime is produced; now, in the urine of paroxysmal hæmoglobinuria, we have undoubtedly a concentrated solution of urates, for I have demonstrated both the facts and their causation over and over again; we have probably also sulphuretted hydrogen in this urine, and the point of greatest interest is the way in which this sulphuretted hydrogen is produced.

Dr. Brunton points out that the sulphuretted hydrogen, which produces the oxalate crystals in the urine, is generally formed in the intestines during digestion of cabbages and other food rich in sulphur, and the way in which it comes to be produced in the intestines, in the paroxysm of hæmoglobinuria, is, I think, a point of great interest.

In chapter vii. I have pointed out, in answer to the arguments of Messrs. Herter and Smith, of New York, on the causation of epilepsy (*New York Medical Journal*, August and September, 1892), that the intestinal putrefaction of which they noticed so many signs in this disease was the simple and constant result of an excess of uric acid in the blood; and I argued that the excess of urate in the blood which obstructed all the capillaries and raised blood pressure to the extent of interfering with the intra-cranial circulation and producing the fits, would interfere also with gastro-intestinal digestion and absorption and allow putrefactive processes to take their place. I doubt not also that a precisely similar explanation may be given of the excess of bacteria in the intestine, and the poison found in the urine as a result of their activity in cases of pernicious anæmia (see Dr. Hunter, *Lancet*, 1891, vol. i., p. 260). Here also the uric acid in the blood is the first thing, while the bacteria in the intestines, and any products they may generate, are secondary, and as in the parallel case of epilepsy unimportant (see also a paper on "Hydrothionuria" in the *New York Medical Journal* of June 17, 1892). This in many cases accompanied digestive trouble or disease, and it is said that it (sulphuretted hydrogen) may also be formed by bacteria in the urine.

Messrs. Herter and Smith say (previous reference), "We cannot say why there should occur in epilepsy so considerable a proportion of cases in which there are evidences of excessive intestinal putrefaction." To my mind the explanation seems as simple as it is complete; and I would suggest that a similar explanation can be given of the presence of oxalates in the urine of hæmoglobinuria; for here also we have collæmia and general obstruction of capillaries, and while the excess of uric acid is causing the blood destruction, the obstructed capillaries suspend gastro-intestinal digestion, and

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putrefaction, doubtless, with the formation of more or less sulphuretted hpdrogen, takes its place. A certain amount of that sulphuretted hydrogen passes with the excess of urates in the concentrated urine, and the frequent presence of oxalate crystals in this fluid is thus fully explained. Lastly, the explanation throws backwards a most interesting light on the actual causation of paroxysmal hæmoglobinuria, and demonstrates that it is contemporaneous with the presence of an excess of uric acid in the blood and urine, and deficient circulation in the intestines which we cannot see, as well as in the skin and extremities producing the symptoms of Raynaud's disease, which we can see, and which are well known to be so frequently associated with it. (For a case in which sulphuretted hydrogen was formed in a dilated stomach, see *Centralblatt fur Inner. Med.*, December, 1894.)

Diagnosis.—Anæmia associated with excess of uric acid in the urine and probably scanty urine as in the case of A. P., fig. 49, and associated with these will probably be dyspepsia, dysmenorrhœa, heavy work or other cause of excessive fatigue, *i.e.*, causes which tend to bring excess of uric acid through the blood whenever such excess is available in the body; thus what is called a "heavy place" is a very common contributing cause of chlorosis in young servant girls, and we already know the relations between fatigue and collæmia.

When anæmia occurs in such association with excess of uric acid in the urine and blood, we can treat the collæmia with full confidence of success, for we now know and can demonstrate that the collæmia is the cause of the blood changes, and not, as was previously supposed, their result.

For treatment we must as far as possible reverse the conditions that produced the trouble, and remove the causes of excessive fatigue or dyspepsia.

But if diet clears the blood of uric acid (1) by stopping introduction at once, and (2) by allowing the gradual elimination of the uric acid already in the body, it follows that we ought to be able to cure chlorosis by diet alone without any drugs like iron, which directly clear the blood of uric acid, but provide also for an almost certain relapse, in that they do not remove the uric acid from the body, but store it up in the tissues.

And I now show in fig. 52 the results of an attempt I made to do this in the case of a girl of 16 under my care in the Metropolitan Hospital.

At the beginning of the figure her blood decimal was found to

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be slightly above 0·3, and she presented all the ordinary signs of chlorosis. She was put on a milk diet with a little fish, and no drugs were given.

Her blood decimal remained at exactly the same level in the two following weeks, in spite of nursing and rest in bed, and then on November 28 the fish was left off.

On December 5 there was a decided fall in the decimal, and the patient had begun to suffer from headache, both being, no doubt, the result of the passage of some excess of uric acid through the blood: I would refer to a somewhat similar fall in the blood decimal produced by a similar change of diet, *i.e.*, from meat to milk and fish in fig. 47 (June 19 to 22 and remarks on this). No doubt the change from meat to fish and milk produced a fall in the acidity of

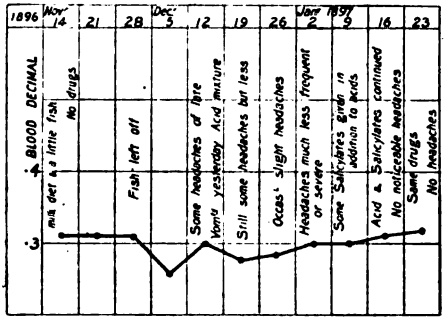

FIG. 52.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING THE EFFECT OF A URIC ACID FREE DIET.

the urine, and allowed the passage of some excess of uric acid through the blood, and similarly in fig. 52 the leaving off the fish produced a fall in the urinary acidity and so some excess of uric acid in the blood, and a fall of the blood decimal, the same result being further indicated by the onset of headaches.

The blood decimal recovers a little on December 12 (fig. 52), but falls again on the 19th and 26th, the headaches continuing in spite of an acid mixture, and then it steadily rises to the end of the figure, the headaches being much less frequent and severe by January 2, and some salicylates being taken in conjunction with the acids on January 9 and onwards.

Now, my object in giving this figure is to show that the first effect of leaving all animal food out of the diet, is a fall in the blood

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decimal, and that this fall is due to the passage through the blood of some of the excess of uric acid in the body, and this is further shown in this particular case by the onset of headaches, and we may note also that as the headaches got less the blood decimal steadily improved.

I may say that this patient went on for some months beyond the end of the figure slowly improving; then she began to lose weight slightly, and it was then found that she was not taking her milk and farinaceous diet at all well, and so she was put back on to ordinary diet, and given iron, under which she improved more quickly, and in a few weeks was able to go out.

I will merely remark with regard to this that the quickest way out of chlorosis is to give iron, mercury, copper, zinc, or any other metal that quickly clears the blood of uric acid, but then a relapse is a matter of certainty, a longer or shorter time (generally within six months) after the metal is left off.

To cure entirely by diet, however, is, as shown in the above case, often very tedious, and there will probably be a more or less decided fall of the blood decimal at first, which may lead to complaints on the part of the patient and her friends; the cure, however, though slow, is certain, and there is no relapse.

I believe, however, that the best way to cure chlorosis is to combine the treatment by diet and drugs in the following way.

When the patient first comes under treatment, give ordinary diet, remove dyspepsia if present by means of bismuth and sodii bicarb. with a saline (sulphate) purge if there is constipation, and then go on to give any of the above metals, it matters little which; I got just as good results with copper or iodide of mercury as with iron. I regard the mercuric salt as the most powerful,[1] but then there is the chance of iodism, mercurialism, and intestinal irritation, the copper also may cause colic and intestinal trouble. Iron is probably the least powerful as regards the blood, but it is somewhat less liable to cause gastro-intestinal trouble than the other two.

When by means of one of these metals the blood decimal has been got up to ·5 or ·6 or above, give salicylates, say every alternate week for six, eight or twelve weeks to clear out the uric

[1] For a record of a case of severe anæmia successfully treated by injection of bichloride of mercury and bichloride of quinine, see *British Medical Journal* Epitome, 1896, April 11, p. 59, and for a case of pernicious anæmia similarly treated with mercury and cured, see the same journal, 1896, Epitome, July 18, p. 11.

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acid, and towards the end of this time reduce and leave off all animal foods, altering the diet to that advised in chapter xvii. The patient is now quite well, and as long as she remains on a uric acid free diet will continue to be so.

Thus Ellen W., aged 23, was under my care in the spring of 1896 in the Royal Hospital for Children and Women suffering from relapsing chlorosis; after treating her with iron as in some of the preceding figures, I let her go out after showing her my diet and telling her that if she would take care to follow it she would not have any further relapses.

She returned as an out-patient on February 18, 1897, on account of some little dyspepsia, due apparently to her eating a large amount of baker's bread, and suffering in consequence from constipation. She told me that ever since she left the Hospital she had been doing as I told her, and living (though not quite as I told her) on nothing but bread and milk. But her blood was a picture; I have never seen such blood in a woman of her age (and she said that all her friends remarked on her fine colour), and indeed I do not think in any man or woman of any age, and it was the only blood I had seen for months and months that would have any chance of comparing favourably with my own.

Here then we have both constipation and dyspepsia existing with the most magnificent blood, and the reason is simple, there is no uric acid in the body, and there has been no introduction in her food, and therefore dyspepsia cannot bring it through the blood.

I have also heard from Dr. Mackie, of Nottingham, that he has got some most interesting and successful results in the treatment of anæmia in young women, by applying my suggestions as to diet.

I have recorded the improvements in my own blood that resulted from leaving off meat, and more recently from leaving off all animal food except milk and cheese; and in every case where I have altered the diet for headache, epilepsy, mental depression, or other similar troubles, there has been a similar distinct improvement in the condition of the blood as one of its results. This generally first shows distinctly about the end of the first three months, and is greater at the end of 6, 9 and 12 months, till at the end of 12—18 months, a blood which was at first under ·5, reaches my own level ·7, and above up to ·8.

In many cases, no doubt, there is a fall of the blood decimal as in fig. 52 on first going on to the diet, but this will vary a good deal with nutrition, and will be less marked where nutrition is good and is adequately maintained on the new diet, and more marked where,

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as in the case in fig. 52, nutrition is poor and is not well kept up on the new diet.

Then during this primary fall of the blood decimal, if the patient suffers from headaches they will be worse, if from fits they will be more frequent and severe, and mental depression will increase, so that both patient and doctor may become disheartened and give up the diet. But to be forewarned is to be forearmed, and by looking carefully after nutrition this primary fall may be diminished, and as regards the headache, fits and depression, it is but one more proof that they are due to the uric acid in the blood, and that patient perseverance in clearing it out and keeping it out will eventually be crowned with success.

These and similar experiences have led me to suggest that in the treatment of headache, fits, mental depression, &c., by diet it may be well to examine the blood every few weeks, or oftener, so as to have a guide to the effects of the diet on the excretion of uric acid and the amount passing through the blood; a weekly examination of which will do practically as well as a more frequent examination of the urine.

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CHAPTER XIII.

Albuminuria and Bright's Disease.

One of my first papers on the uric acid headache (*Practitioner*, March, 1886) ends as follows:—"And further, as it is by no means uncommon to find in the *post-mortem* room that there are urates in the joints of persons who are not known to have had manifest gout, and that such urate deposits are often associated with granular kidneys, hypertrophied heart, degenerate vessels, and cerebral hæmorrhage, I think that many people who have the forms of headache and the history above described, and are easily affected by butcher's meat, and, indeed, resemble cases of Bright's disease in the manifest benefit they often derive from leaving it off altogether; I think that many of these cases tend to degenerate in this direction as years go on, and perhaps, finally, to enter the *post-mortem* room under some or all of the conditions above mentioned. So that I am inclined to believe that the diet treatment of these forms of headache may mean much more than the alleviation of their pain, and that if it is fortunately begun early in life, it may possibly be the means of preventing, or greatly delaying the more serious and fatal developments."

I believe now much more strongly just what I was beginning to see then, that from the uric acid headache to chronic Bright's disease, the only change is one of degree, and I see no reason to doubt that if I had not altered my diet thirteen years ago, I should to-day be suffering from albuminuria.

Since I wrote the lines quoted above, I have seen quite a large number of cases in which periodical sufferers from the uric acid headache have come to suffer from albuminuria and chronic Bright's disease; and even at this moment I have under my care several cases, of which I shall presently give a few notes, and in which I believe that the transition from migraine to morbus Brightii is occurring before our eyes.

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The alteration in my diet has not only prevented my having a headache more than two or three times in a year (in place of forty to fifty times), but it has rendered the attacks in every respect less severe, the coldness of the skin and extremities is much less, the pulse is almost never as slow or of as high tension as it used to be; so that a rate below 60, or tension as high as that shown in fig. 37 is now quite rare, and my general level of blood pressure has, I believe, been lowered to a corresponding extent. Thus the circulation and metabolism in my skin and other important organs has not been hindered to anything like the extent it would have been had I continued my meat diet during these years, and I have so far, therefore, escaped albuminuria and Bright's disease.

Though I never found any in my own case, I believe it is by no means very rare for sufferers from the uric acid headache to have a little albuminuria at the time of the attack or just before it is over, and some sufferers have albuminuria with their bad attacks, but not with their slight ones. My experience in this respect is by no means singular; as I notice an article by Dr. Stewart Lockie, in the *British Medical Journal*, 1886, vol. i., p. 1059, on the albuminuria of adolescence and headache as its chief symptom. He also mentions the frequent presence of a gouty family history in these cases.

The analogy between cyclic albuminuria and migraine is also pointed out in a paper abstracted in the Epitome of the *British Medical Journal*, 1896, June 6, p. 89.

Then again it will have been gathered from what I said of paroxysmal hæmoglobinuria in chapter xii., that I look upon it simply as a paroxysmal fluctuation in urate excretion, entailing the passage of an excess of uric acid through the blood. It is in fact a severe uric acid storm, and the headache in this case, just as in the cases of albuminuria mentioned above, is very frequently present.

Then also it will be understood that I believe there are to be met with all gradations from the blood changes of anæmia produced by uric acid, to the hetero-albuminæmia (Semmola) and albuminuria, and finally to the hæmoglobinæmia and hæmoglobinuria, of the paroxysmal disease; the factor immediately underlying these blood changes being a deficient circulation in the skin and other important organs of metabolism, and behind this again, and the cause of all subsequent changes, is an excess of uric acid in the blood.

The obstructed capillaries, which raise on the one hand the pressure in the arterial system, diminish, on the other hand, the

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circulation through all the organs and tissues of the body; headache, mental depression and fits, represent, probably as we have seen, the effects of the high blood pressure on the intra-cranial circulation, while arterial degeneration and hypertrophy of the heart are some of its effects on the vascular system; on the other hand, the cold skin and extremities, certain alterations in the skin and other structures up to Raynaud's disease, and the atrophied skin of Bright's disease, and certain changes in the blood, and circulating albumens from anæmia to hetero-albuminæmia and hæmoglobinæmia, these being accompanied by diminished formation of urea just as we have seen it falling in fatigue (figs. 39 and 40), and indeed wherever, even in physiological conditions, there is an excess of uric acid in the blood, represent the effects of the defective circulation on the great metabolic tissues, where the combustion of the body is carried on.

In so far as these changes are due to uric acid, they are at first functional and may be completely recovered from, but when the uric acid storm is severe, and repeated every week for years, the interference with circulation is sufficiently great and prolonged to produce atrophy and degeneration of tissues, and then the full picture of Bright's disease gradually unfolds itself, and complete recovery is no longer possible.

The only course now is to reduce the metabolic needs of the body within the limits which atrophied structures may suffice to perform, just as occurs sometimes in phthisis, when a patient may last for years with only a lung and a half, or less, because the respiratory needs of the body have been correspondingly reduced.

In saying this, it must not be lost sight of that external conditions, such as temperature, will very greatly influence in one way or another the effects of uric acid on the skin circulation; while an internal condition, such as dyspepsia, by keeping up for weeks and months a more or less severe collæmia (see chapter x.), may bring into existence, in a comparatively short time, its worst effects on metabolism and nutrition. My clinical observation leads me to believe that chronic Bright's disease, and possibly also the nearly allied condition of myxœdema, not very rarely take origin in this way from chronic dyspepsia.

See also a paper by Dr. Tirard in the *Lancet*, 1896, vol. ii., p. 377, on dyspepsia as a predisposing cause of Morbus Brightii; but it is far more than a predisposing cause; it is one link in a chain of causation and itself also a result of collæmia which it helps to continue and intensify.

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The best proof that uric acid exerts the effect on the vessels, which this pathology postulates, is I think to be found in the fact (previously gone into, chapters ii. and iii.) that the urinary water varies from hour to hour, and day to day, inversely as the uric acid excreted along with it, and the further fact that very numerous drugs which diminish the uric acid increase the water, while others which increase the uric acid diminish the water.

Add to this that excess of uric acid in the blood diminishes the formation of urea both in physiology and pathology, and determines the onset of fatigue (chapter viii., figs. 39—42), and we have some pretty convincing proofs of its great and far reaching powers over the metabolism and combustion of the body.

As some appear to have misunderstood the bearing of my remarks on the circulation of the kidney (Sewall, *Medical News*, Philadelphia, Sept. 16, 1893), I may perhaps do well to re-state them here.

It is no doubt quite true, as this observer points out, that physiological experiment has shown that the blood supply of the kidney varies directly with arterial blood pressure; but in these experiments the capillaries of the kidney remained neutral, whereas my point is that in collæmia the capillaries of the kidney are not neutral, but like the vessels of the skin, the eyes, and the salivary glands, they are more or less decidedly obstructed; and what I suggested was that this obstruction overcame the power of arterial blood pressure to force blood through the kidneys, and the remarks I have quoted from Dr. Lauder Brunton (p. 145) show, I think, that this is his opinion.

Clinically I think we meet with scanty urine under two conditions: (1) when the heart, being normal, the obstruction of capillaries is abnormally great, and the kidney circulation is consequently defective; (2) when the obstruction of capillaries is not above normal, but the heart is weak or diseased, and has not the power to drive the blood through them.

The failure of circulation is, in both cases, due to the fact that the heart has not power to do what is required of it; but a finger on the pulse will enable us in a moment to distinguish between them, for in the first case there will be high blood pressure, in the second almost none; the same argument applies to the circulation in all the tissues of the body, and I have already alluded to it in connection with the incidence of Raynaud's disease on girls and women (p. 374).

This also explains completely the absence of dropsy in chronic Bright's disease, for in this disease the heart at first hypertrophies

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and works up to its troubles, but when, later on, its nutrition with that of the whole body suffers severely, it fails and dilates, and then retention of water and dropsy quickly supervene, because the capillaries in the kidney and elsewhere get the best of it.

When anything, such as previous pericarditis, prevents the heart from undergoing this conservative hypertrophy, the primary dropsy is marked and persistent, and the end is so rapid that there is no time for chronic changes in the kidney to take place.

Having thus given an outline of the position I have been gradually led to take, with regard to the causation of albuminuria and Bright's disease, I shall now give a little more in detail some of the facts on which it is founded.

In a paper on "The Connecting-link between the High Tension Pulse and Albuminuria" (*British Medical Journal*, 1890, vol. i., p. 65), I mentioned certain points which seemed to me of interest in connection with the writings of the late Dr. Mahomed and those of the late Professor Semmola, as bearing upon the causation of the disease, and suggested that hetero-albuminæmia, of which the latter writes, and to which the kidney lesions found *post-mortem* are secondary, gave us a good explanation of the causation both of Bright's disease and of so-called functional albuminuria.

I will now mention a few of the points in this paper.

The late Dr. Mahomed pointed out that though a high tension pulse is a common and characteristic feature of Bright's disease, it might nevertheless be present for several years before there is any albuminuria. He said that the high tension and other signs of what he called the pre-albuminuric stage of Bright's disease were probably due to a poison in the blood, and I suggested that many of the signs and symptoms he spoke of were those of collæmia, and that the poison he was in search of was probably uric acid.

Dr. Mahomed also showed that in certain cases of temporary albuminuria, about which I shall have to speak at greater length presently, the appearance of the albumen was preceded and accompanied by an increase of arterial tension.

I then quoted at considerable length from the works of the late Professor Semmola, who shows that the appearance of albumen in the urine is due to the presence of an excess of diffusible albumen in the blood (hetero-albuminæmia), the kidney lesions found after death being due to the irritation which this foreign albumen eventually sets up in passing through its glomeruli and tubules.

I pointed out in support of Semmola's thesis that Stokvis in one of his experiments with egg albumen did produce some kidney

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irritation, resulting in the passage of serum albumen into the urine.

I pointed out that taking Bright's disease as a primary alteration (inflammation) of kidney structure causing serum albuminuria, there is nothing to account for the excess of diffusible albuminoids in the blood as to the existence of which in nephritis the observations of the late Professor Semmola do not stand alone.

I further said, that while the theory of primary kidney lesion quite failed to account for the clinical symptoms of many cases of so-called "functional" albuminuria, the theory of primary blood lesion (hetero-albuminæmia) might account for them completely.

The chief arguments of the late Professor Semmola are as follows, and I take them from the work of Dr. Labadie-Lagrave (*Urologie Clinique et Maladies des reins*, Paris, 1888, p. 714, *et seq.*), so as to give my readers the opinions of others, rather than my own, on the work of Professor Semmola.

(1) The amount of albumen in the urine varies with the amount of albumen in the food and not with the renal lesion; therefore the albuminuria is not due to the renal lesion.

(2) The cause of Bright's disease is the action of cold and damp on the skin, but this cold and damp in chronic cases is not able of itself to determine hyperæmia of the kidney; that is to say, the lesion eventually found in the kidney is not the direct result of the action of cold and damp on the skin, therefore there must be some intermediary.

(3) This intermediary is unassimilable albumen; certain portions of the circulating albumens being rendered unassimilable and diffusible by failure in the metabolism of the skin.

(4) This unassimilable albumen is eliminated by the kidneys and other organs, and gradually produces irritation and parenchymatous and interstitial changes in their structure—Bright's disease.

Thus Labadie-Lagrave says (previous reference, p. 719), "Ainsi donc: accumulation dans le sang d'albuminoides inassimilables: premier fait et consecutivement lesions renales. Tel serait d'apres Semmola l'en chainment du processus dans le mal de Bright."

He then points out that as a result of this doctrine there must be from the very outset a diminution of urea; and that Semmola has long pointed out this diminution, and also the fact that it is due to diminished formation as the amount of urea in the blood in early Bright's disease is less than in healthy blood, so that there is no accumulation, nor is there any increase of creatin, creatinin, or other intermediate nitrogenous products.

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I have also pointed out in chapter iv., the way in which collæmia, by interfering with the circulation in the liver, muscles, skin, &c., may hinder metabolism, and lessen the formation of urea, and the further fact that the formation of urea, as well as the symptoms of fatigue, can be controlled by controlling the collæmia; here, indeed, we have in fatigue an epitome of Bright's disease, prolong the collæmia over weeks and months, and we have to deal with actual Bright's disease, which again, while recent, can also be controlled in exactly the same way that fatigue can be, and with the same drugs, or even the same metal (mercury).

But this theory of hetero-albuminæmia is no mere hypothesis, for Semmola bleeds his patients, and demonstrates that their blood contains excess of albumens that diffuse; also that blood which contains this excess will produce albuminuria when injected into a dog, and this albuminuria will be proportional to the amount of diffusible albumen in the blood injected.

Labadie-Lagrave (previous reference, p. 727) further points out that Semmola has shown that in Bright's disease there is not only anæmia of the skin, but that its glands, epithelium, and cells of the Malpighian layers have undergone most extensive atrophy, this doubtless carrying with it great interference with function and healthy metabolism; while in albuminuria due to other causes, as morbus cordis, alcoholism, gout, there is no alteration whatever in the structure of the skin, and he concludes his notice as follows:—"Telles sont les derniers recherchés toutes recentes du professeur Semmola, qui viennent si brillamment a l'appui de la theorie dont il est l'ardent défenseur" (p. 728).

On this theory an albuminuria is on all fours with a glycosuria. No alteration of kidney structure has been suggested to account for the latter. On the contrary, it is known that any excess of sugar in the blood at once passes off by the kidney, and that this sometimes causes hyperæmia and irritation of the kidney. On Semmola's theory albuminuria is due to excess of diffusible albumen in the blood, and this, in its passage through the kidney, causes more severe irritation and nephritis.

Lastly, I pointed out that uric acid (the poison of which Mahomed noted the effects, and which I identified from the clinical symptoms it produced) might bring about hetero-albuminæmia, with secondary albuminuria and nephritis, and thus form the connecting link between the high tension pulse, etc., of the pre-albuminuric stage, as observed by Mahomed, and actual Bright's disease.

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I suggested that uric acid by obstructing the capillaries (as it does when it raises the tension) might interfere seriously with the metabolism of albuminoids both in the liver and the skin (which accords with Semmola's facts as to the causation of hetero-albuminæmia), and that when this action is very intense we might get breaking up of hæmoglobin itself as in paroxysmal hæmoglobinuria (the most intense condition of hetero-albuminæmia), the symptoms accompanying which I pointed out are just those of a uric acid storm (collæmia).

On the other hand, I pointed out that the violent action of uric acid on the capillaries might account for that disease which is most nearly related to paroxysmal hæmoglobinuria, and like it is accompanied by marked clinical signs of collæmia, namely, Raynaud's disease; and that the symptoms of the pre-albuminuric stage according to Dr. Mahomed, are cold hands and feet, imperfect digestion, bronchitis, gastric catarrh, headache (especially hemi-cranial), loss of memory, depression, weariness, cloudiness of intellect and hypochondriasis, and after what I have said in previous chapters as to the causation of these symptoms by uric acid I must leave my readers to judge of their meaning.

We can now also see in reference to Semmola's facts as to the effects of cold and damp on the skin, that these may not only, as he supposed, directly contract the vessels of this important tissue, but by precipitating a collæmia, just as in the test-tube (see p. 148), may still further hamper its circulation, nutrition and metabolism, especially in those who have on the one hand much uric acid available in the body, and on the other a heart which (as so often happens, in pregnancy, for instance) is weak relatively to the increased work required of it.

It seems then that at this point we have three chief theories as to the causation of albuminuria:—

(1) That it is due to heart failure (which applies, I suppose, only to temporary albuminuria and not to Bright's disease).

(2) That it is due to irritation of the kidney by a poison in the blood (Mahomed).

(3) That it is due to hetero-albuminæmia, just as glycosuria is due to glycæmia, and that irritation and structural change in the kidney are secondary (Semmola).

And to this last I have added the suggestion that, while hetero-albuminæmia may be due to the action of cold on the skin, the obstruction of vessels which uric acid produces may bring about very similar effects, or at least greatly increase the power of cold.

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Then in the *Guy's Hospital Reports* of 1881, we find Dr. Mahomed speaking of cases of nephritis, and also of convalescence from scarlatina, in which there is no albumen while they are in bed; but it occurs on getting up and going out; and with reference to this he says (p. 416), "The rapidity of the change is too great for the kidney condition, determining it to be a structural one; it must be functional, or more probably a vascular phenomenon. The fact stands, therefore, that the same kidney, and that a diseased one, can produce alike normal and albuminous urine." This observation, it will be noted, is in complete accord with that of Semmola quoted above, that the albuminuria does not correspond with the kidney lesion.

I do not deny that certain vascular conditions can produce albuminuria (notably congestion in severe morbus cordis), but I do deny that cardiac weakness and congestion accounts for the albuminuria in the cases of so-called functional albuminuria mentioned in my paper in the *British Medical Journal*, January, 1890, p. 65, or for temporary albuminuria in cases of chronic Bright's disease such as those spoken of by Dr. Mahomed.

I also deny that uric acid in the blood directly irritates the kidney and produces albuminuria and eventually nephritis, though I have no doubt that an accumulation of urates, or for that matter of pigment or other matters in the kidney, or even the mere passage through it of sugar or bile, cantharides, &c., may produce congestion and slight albuminuria, but that is in many ways a very different matter from nephritis. Urates also may accumulate to a large extent in the kidney just as they do in the joints and other fibrous tissues—"gouty kidney"—but this also is probably a different thing from parenchymatous and interstitial nephritis.

As to heart failure, there is no doubt that this may produce congestion of the kidney and albuminuria. Semmola himself admits this, but he points out that when albuminuria is due to this cause the blood does not contain any excess of diffusible albumen, which at once distinguishes cardiac cases from those of Bright's disease; and cardiac kidneys are generally easily differentiated from those of Bright's disease *post-mortem*.

In transitory albuminurias in apparently healthy subjects not due to mechanical causes, in albuminuria in the course of *maladies dyscrasiques*, and in the albuminuria of convalescence from scarlet fever, Semmola finds excess of diffusible albumen in the blood—an excess which is proportional to the amount of albumen that is eliminated in the urine.

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Mahomed's theory regarding the local irritation in the kidney produced by his hypothetical poison as the cause of albuminuria and Bright's disease fails to explain two points of great importance in that disease: (1) Semmola's excess of diffusible albumen in the blood, and (2) the diminished output of urea which is generally acknowledged to accompany or even precede the onset of Bright's disease.

As Semmola remarks, his hetero-albuminæmia gives the best possible explanation of the diminished urea, for if albumen is not metabolised but excreted unaltered, the formation of urea must obviously be reduced.

I would also remind my readers again that in all collæmia there is a diminished formation and excretion of urea, and that from my point of view chronic collæmia is equivalent to the pre-albuminuric stage of Mahomed, and leads inevitably to chronic Bright's disease, so that I can easily account for the diminished urea.

But if these theories fail, let us see how far the theory of hetero-albuminæmia will carry us in explaining the history and symptoms of Bright's disease.

Semmola says that anything that interferes with the functions of the liver or the skin may hinder the proper metabolism of albumens and produce hetero-albuminæmia, which he regards as the first stage in the causation of albuminuria and nephritis.

I have suggested that uric acid, by its action on the capillaries, may interfere in the way sketched out above with the functions of the liver, and by obstructing its capillaries, as it clearly does during an attack of uric acid headache, may also seriously interfere with the functions of the skin; hence, in accordance with Semmola's reasoning, it may produce hetero-albuminæmia and albuminuria. (See also chapter iv.)

I pointed out in my paper on albuminuria (previous reference) that the theory of heart failure would not explain the cases described by Dr. Dukes (*British Medical Journal*, 1889, vol. i.), in which, in association with high tension pulse, there was albuminuria when the patients were up and about, except when they were on milk diet; but no albuminuria when they were in bed, no matter what diet they were given. These cases differ from those of Mahomed previously mentioned in that another factor in causation (namely, diet) is introduced. Mahomed's cases might have been due to heart failure, because the albumen appeared when they were up and about, and disappeared when they were in bed; but in Dr. Dukes' cases the patients might be up and about, and yet have no

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albuminuria so long as they kept to milk diet; and it appears to me to be nonsense to say that the heart failed on ordinary diet, but did not fail on milk. Hetero-albuminæmia, however, will explain these cases easily, for milk is, according to Semmola, the form of albumen which requires least elaboration by the skin, and I have suggested that this is due to the fact that it is really the product of a skin gland; then again, they have no albuminuria while in bed, no matter what diet is taken, because the warmth of the blankets relaxes the vessels of the skin and counteracts the effects of uric acid.

I have also spoken of the albuminuria that sometimes follows a cold bath, and have suggested that it is due to hetero-albuminæmia following the contraction of the vessels of the skin by cold, more or less aided by uric acid, which is generally in excess in the urine and blood in the morning hours; heart failure, again, seems to me an inadequate explanation, as the heart has just had the benefit of a night's rest and recuperation.

Again, in Dr. Dukes' cases the albumen is excreted in greater quantity after meals, especially after breakfast, than at other times of the day. Why should the heart fail in the morning after breakfast more than at any other time?

In a more recent paper (*Lancet*, 1891, vol. ii., p. 1327) Dr. Dukes attributes to more or less chronic congestion of the kidney the albuminuria of adolescents, and the Bright's disease into which he thinks it may eventually develop; but as I have before remarked a congestion of the kidney will not explain an excess of diffusible albumen in the blood or a diminished formation of urea.

My explanation of Dr. Dukes' cases is collæmia producing obstructed vessels and high blood pressure, hampering the functions of the liver or skin, or both, producing hetero-albuminæmia and albuminuria; and the albuminuria is most marked at those hours at which, in the natural physiological cycle, the collæmia is most intense, the pulse slowest, and the urinary water lowest (see figs. 2 and 3). Dr. Saundby points out ("Lectures on Bright's Disease," p. 15) that in Bright's disease also the albuminuria is greatest after meals, and especially after breakfast, and in one or two instances in which I have been able to examine the point this has certainly been the case; so that these "functional" cases resemble, in this respect at least, the organic disease, and I for one am quite ready to believe that they may pass into it.

Now let us look at the etiology of acute Bright's disease. Sir W. Roberts says ("Urinary and Renal Diseases," ed. iv., p. 471):

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"That complex of impressions, which is familiarly known as taking cold, is the common cause of Bright's disease in its acute form;" and in common with other writers he mentions also scarlatina and alcohol.

Now I hope that after what I have said in previous chapters it is unnecessary again to point out the way in which all these factors act in producing a fluctuation in the excretion of uric acid, the fluctuation resulting in the production of more or less severe collæmia which brings about, we are supposing, hetero-albuminæmia, albuminuria, and nephritis.

I do not deny that high blood pressure and obstructed capillaries, which interfere with the circulation in the kidney and produce scanty urine, do probably, to some extent, also interfere with its nutrition, and that where such high tension is very frequently present the interference with nutrition may be carried to the extent of producing structural change; but granting all this we are no nearer to an explanation of Semmola's facts—the excess of diffusible albumen in the blood, and the diminished formation of urea in Bright's disease.

In the *Wien. Klin. Rund.*, January, 1895, the late Professor Semmola again puts forward some of the main points of his important researches, such as the fact that the subcutaneous injection of egg albumen in dogs causes albuminuria, which is not at first attended by any histological changes in the kidney, and draws the conclusion that egg albumen can pass through the kidney without there being any lesion of its epithelium present. But continue the passage of albumen through the kidney for more than forty-eight hours and hyperæmia and progressing chronic nephritis ensue.

Here we have produced experimentally exactly what we see occurring almost daily before our eyes in nature; thus a man may have migraine every week for a long time and the passage of a little albumen for a few hours at the worst part of the attack may produce no change in his kidney whatever; but if his collæmia becomes more chronic, and if the albuminuria is continued from day to day or even week to week, the result is very different. The patient perhaps tells you that during the last month or two his headaches have been more frequent and severe, and you examine his urine and find distinct evidence of kidney lesion.

In these two months the change has been made from functional to organic, from migraine with temporary albuminuria, to Bright's disease with chronic albuminuria, and though we can still control the uric acid and the hetero-albuminæmia and functional albu-

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minuria, the high blood pressure and the headaches it produces, we cannot put back the damaged kidney structure or prevent the passage of serum albumen through its injured tissues, or reinstate in their original integrity the skin, muscles, liver, the great metabolic tissues which are similarly damaged.

Such cases, I believe, occur daily under our very eyes, and only the mists of erroneous pathology have hitherto prevented our seeing them. So far as they are functional true pathology gives us complete power to control them, and even the kidney lesions tend to repair themselves if the cause of irritation is removed before the damage is too great.

The late Professor Semmola also points out that the amount of albumen eventually excreted in these experimental injections corresponds in no way with the amount of albumen injected, nor yet with the extent of the kidney lesion, but rather with a change in the composition of the blood itself, which makes its serum albumen morbidly diffusible; or in other words, the continued injection into the skin of an abnormal albumen eventually brings about such changes in metabolism and nutrition that the blood serum itself becomes imperfectly elaborated or metabolised, and in consequence abnormally diffusible.

In any case the quantity of albumen excreted in Bright's disease depends on these blood conditions, and not at all on the extent of the kidney lesion, just as in paroxysmal hæmoglobinuria we get an enormous quantity of albumen with blood changes, but no kidney changes in proportion to it.

On the other hand, in the case of direct kidney lesions, such as those produced by cantharides, the amount of albumen is small compared with the kidney lesion.

Semmola says that continued injection of egg albumen eventually produces albuminuric retinitis, and that true Bright's disease can be artificially produced in this way; also that in acute infectious diseases, toxic, rheumatic and gouty dyscrasias, the albuminuria is due to modifications in the diffusibility of the albumen of the blood.

And the facts with regard to the presence of these diffusible albumens in the blood in Bright's disease, or at least, in certain stages of Bright's disease, seem to be confirmed by the researches of Freund, and have been accepted by Vulpian, Labadie-Lagrave, and others I have quoted. But I shall have more to say on these points when I come to deal with cases.

Now cold raises acidity, fever raises acidity, most alcoholic

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drinks raise the acidity, and these last, acting over long years, hold back and retain in the body large quantities of urate which provide the material for eventual chronic and severe collæmia in old age or other failure of nutrition; and this collæmia is to my mind the cause of the chronic nephritis so often found in the *post-mortem* room with chronic gout (see Dr. Norman Moore, *St. Bartholomew's Hospital Reports*, vol. xxiii., p. 289). Further, the excess of urates which under these conditions passes into the blood and out in the urine, is the cause of the gravel and calculus so frequently met with in the declining years of life (compare also case mentioned on p. 43).

But where the collæmia is more sudden and severe as when it results from sudden severe chill (a case under my care got his disease by being called from the stoke-hole of a steamer to stand twelve hours or more on deck, where he got wet through in five minutes and had to remain so), it may produce not only hetero-albuminæmia; but the urate may, as I have suggested, acting in sequence to the chill, attack also the red cells and cause hæmoglobinæmia and hæmoglobinuria, and it appears that in some cases paroxysmal hæmoglobinuria has formed the starting point of acute Bright's disease (*Lancet*, 1889, vol. ii., p. 1007).

With regard to the causation of paroxysmal hæmoglobinuria, Sir W. Roberts says (*loc. cit.*, p. 162): "Most observers are now agreed that the solution of hæmoglobin in the serum precedes its appearance in the urine, and that the symptoms of kidney affection which are sometimes present are due to the irritation produced by the passage of the hæmoglobin through these organs."

Here, then, in the case of paroxysmal hæmoglobinuria the whole of Semmola's contention is quietly admitted; first of all that the escape of the blood constituents in the urine is due to their breaking up in the circulation itself, and second, that their passage through the kidney causes irritation in that organ.

If it is granted that in place of such violent and temporary destruction of blood elements we may have severe hetero-albuminæmia lasting continuously over several days (less intense, but of longer duration), may we not see in this the causation of acute Bright's disease as it is met with clinically? and there is no difficulty in granting this, as numerous observers (notably Dr. Stephen Mackenzie, *Lancet*, 1884, vol. i., p. 243) have seen albuminuria both preceding and following the hæmoglobinuria.

Further, the albuminuria which accompanies migraine, or epilepsy, or convalescence from acute disease, all conditions in

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which there is often the most obvious and severe collæmia and of which paroxysmal hæmoglobinuria is so clearly a mere exaggeration almost of themselves suffice to demonstrate, that the association of albuminuria with collæmia is no accident, and when we further consider that even in physiology uric acid controls the formation of urea, we can at once understand the fall of urea as seen in the above functional troubles as well as that which is so marked a feature of the onset of Bright's disease.

Then, in Bright's disease, we shall further see that when we clear the blood of uric acid and allow combustion to go on freely, the albumen diminishes exactly in proportion as the urea increases, so that there is not much room for doubt as to the real relation between these two substances.

The following case throws, I think, some light on the causation of albuminuria in the way I am suggesting, by the action of cold or uric acid or both on the vessels of the great metabolic tissues.

E. H., age 44, a patient of Dr. Tomson, of Luton, Beds, to whom I am indebted for the history of the attacks—

Complains of attacks of "liver" every three months or oftener, accompanied by extreme mental depression, shivering and retching, and followed by rise of temperature. Subject to these attacks as long as he can remember.

Had fits at 5 and 12 years of age.

His mother died of phthisis at the age of 50.

His father is still alive and well, age 83.

Two brothers (one an imbecile), and one sister died of phthisis.

One sister has functional twitching and contractions of the muscles of both arms.

Other members of the family exhibit evidences of an insane neurosis.

Patient was operated on for anal fistula in 1892.

The following is Dr. Tomson's account of an attack he saw in December, 1892.

"Condition distinctly hysterical; throws himself about on the couch, and repeatedly cries out 'Oh, I'm so bad! Oh, I'm so bad!' A constant restlessness. He shivers, and the teeth chatter; occasional retching, but nothing brought up; pulse 108; artery contracted, high tension, temperature just under 100°, liver much enlarged three fingers' breadth below the ribs. Urine high coloured; no albumen.

"In this condition he remains for two or three days and then gets better. The more noticeable features are the rapid enlarge-

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ment of the liver, and its equally rapid subsidence at the termination of the seizure, and the intense misery of the patient." He has severe attacks like this about every three months, and less severe attacks between times.

When I saw him he told me that he had had a headache on the previous day, which began at 11.30 a.m.

His pulse was only 54, and both to finger and sphygmograph showed extremely high tension; the first sound of the heart was prolonged or reduplicated between the apex beat and the sternum, and the second sound was loud; he had thus both the cardiac and arterial signs of high tension (p. 187). The liver dulness was not enlarged, and its edge could not be felt; and now we come to a point of very great interest. The urine which he passed here (12 noon) was high coloured and specific gravity 1020, contained a large quantity of albumen, 4 per 1,000 (Esbach), and no sugar. Under the microscope it showed numerous oxalate crystals, and a few casts hyaline and slightly granular. This was the first time albumen had been noticed in his urine.

Let us try to group these symptoms and estimate their meaning. *Obstructed capillaries and high blood pressure* shown in the attack described by Dr. Tomson, in the condition of the pulse, the shivering and teeth chattering, the high coloured and probably scanty urine. The hysterical conditions, and the mental depression are the effects of the high blood pressure on the intra-cranial circulation, just as the shivering may be the effect of the deficient circulation in the skin; I have myself had just such shivering or slight rigors in my attacks of uric acid headache when they used to be severe.

What is the meaning of the marked enlargement of the liver? I would suggest that it is a venous congestion or hyperæmia due to failure of the heart before the high blood pressure; when I saw this patient there was very high blood pressure, but the pulse rate was only 54; there was therefore no sign of heart failure, and with this there was no enlargement of the liver; but in the attack described by Dr. Tomson the pulse rate was 108, and yet he says the tension was high; now such a pulse rate with high blood pressure almost certainly means heart failure, and it is possible that the vessels of the lungs were at the same time greatly obstructed (see chapter ix.), and that this told specially on the right heart and the liver.

What was the cause of the high blood pressure? Excess of uric acid in the blood; the urine was high coloured and probably scanty, and we know that the urinary water is inversely as the

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uric acid excreted along with it; therefore there was excess of uric acid in the urine and probably also in the blood. I look upon these so-called "liver" attacks then as uric acid storms almost if not quite identical with my attacks of uric acid headache, and in these attacks in myself I have often noticed some distinct evidence of more or less temporary congestion of the liver, such as pain, weight, fulness, or a feeling of heat or tension in the right hypochondrium, and these sensations are at their worst when the blood pressure is greatest, and I now rarely or never suffer from them.

Now we come to the trouble at the time I saw him; again the signs of obstructed capillaries and high blood pressure are most marked in the heart and arteries, there was a headache, no doubt the result of this tension, the previous day, and the urine is found to contain a lot of albumen together with some casts and some oxalates, the urine was free from albumen a day or two before, and it became again free from albumen a day or two later.

We have, then, here almost completed the picture, not of paroxysmal hæmoglobinuria, but of the next thing to it, paroxysmal albuminuria.

Now the point on which the whole of this chapter hinges is the way in which this albuminuria was produced; let us look closely at the meaning of the symptoms accompanying it.

A urine of high colour and specific gravity, and therefore almost undoubtedly containing some excess of uric acid. Again, we have seen in the previous chapter that oxalates may mean the simultaneous excretion of intestinal putrefactive products (sulphuretted hydrogen) with an excess of urates; so that here again we have independent evidence that an excess of urates was excreted in this urine, but why was there intestinal putrefaction? Because the vessels of the intestines, like all the vessels in the body, were obstructed by uric acid, the very uric acid which was passing in excess in the urine. Again, we know that the vessels were obstructed on the day before the albuminuria, because high blood pressure was the probable cause of the headache from which the patient told us that he suffered.

We have, then, some very strong evidence of the presence of high blood pressure and obstructed capillaries, and evidence that these had been present for at least twenty-four hours before I saw the patient and found albuminuria. We have also some very good evidence that these capillaries were obstructed, owing to the presence of an excess of uric acid in the blood.

We have seen also in previous chapters that excess of uric acid

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in the blood may not only account for the blood changes of anæmia, but also for those of paroxysmal hæmoglobinuria, and we know that albuminuria may both precede and follow hæmoglobinuria, so that it is extremely probable that hæmoglobinæmia and hæmoglobinuria are but more advanced stages of hetero-albuminæmia and albuminuria.

I am suggesting, then, that the chain of causation in the case of this albuminuria was as follows: a uric acid storm or fluctuation of excretion resulting in collæmia, general obstruction of capillaries, deficient circulation in the skin, liver, intestines, and other organs of metabolism; as a result of this retrograde changes in the albumens of the blood and tissue fluids (hetero-albuminæmia of Semmola), which in some cases may go on to hæmoglobinæmia; but in this case stopped short at hetero-albuminæmia and albuminuria.

Some may say "You spoke of congestion of the liver just now; why may not a congestion of the kidneys similarly produced account for the albuminuria?"

First of all, at the time of this albuminuria, there was no evidence of congestion of the liver, and again even if we grant that there was congestion of the kidneys that would not account for all the conditions; suppose that instead of stopping short at albuminuria the attack had gone on to hæmoglobinuria, how could any congestion of the kidneys account for the destruction of a million red cells in the blood stream itself?

No doubt in congestion of the kidneys due to morbus cordis, for instance, one gets a trace, even a considerable cloud of albumen, but not, I think, as much as in this case, 4 per 1,000.

No congestion of the kidneys can account either for hæmoglobinæmia or the hetero-albuminæmia of Semmola; any such explanation therefore falls to the ground.

Taking the view, then, that this patient's troubles were of the nature of paroxysmal albuminuria, and due to recurrent uric acid storms, the obvious indication was to reduce the uric acid income and formation, I accordingly suggested a considerable reduction in the amount of meat and animal food, and I believe he went beyond my suggestions and became almost a vegetarian. In the six months that have elapsed since this change of diet he has had no attack of "liver," no albuminuria, and is in many other respects much better, and a more recent report says that he has now not had an attack for more than a year.

Thus the treatment seems to have had the very same effect that it had in my own case—with the removal of the cause the effect has disappeared.

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And this is another point on which I wish to lay special stress, namely, that when the diagnosis of uric acid disease has been well and properly made, treatment of the uric acid should without fail effect a cure.

On the other hand, an intentional increase of the uric acid should equally without fail make all the symptoms worse.

Further, it is a distinguishing mark of these metabolic albuminurias that they are greatly influenced by diet, that, as pointed out by Semmola and others, the amount of albumen excreted is to a considerable extent proportional to the amount ingested, and that by reducing this amount and, further, by taking it in a form which is easily assimilated (milk, Semmola), these albuminurias, so long as they remain functional can be greatly reduced or cured; and the experiences of Dr. Dukes quoted above confirm what I am saying.

The parallel between an albuminuria and a glycosuria is here again absolute, both in their early stages are functional, and in both during this stage the whole of the albumen or sugar can be removed. A little later there is a residue in both cases which neither diet nor drugs will suffice to remove; in the interval some of the great metabolic tissues being continually exposed to the results of defective circulation, have undergone atrophy and change of structure, and the furnaces of that human body will never again be capable of consuming quite as much sugar or albumen as they did before.

Supposing, on the other hand, that nothing is done and the patient continues to form and take in large quantities of uric acid, not only will his attacks continue, but they will get more and more severe as he gets older; for the slackening metabolism which comes with age will favour the passage of a larger and larger excess of uric acid through the blood, and thus the metabolic albuminuria, which was at first paroxysmal and functional, will become organic owing to wasting of the metabolic tissues, structural changes will take place in the kidney owing to the constant irritation of hetero-albuminæmia, and so we gradually pass from a mere uric acid storm to fully developed morbus Brightii, and I have seen, as I say, quite a number of cases in which periodical sufferers have found their attacks getting more frequent and severe, and have then, on examination for insurance or other cause, discovered both albumen and casts in their urine.

On the other hand, I have seen quite a number of cases of albuminuria, either temporary or intermittent, where diet treatment

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has almost at once removed the albuminuria and many of its concomitant symptoms, and the cure has appeared to be permanent.

Some evidence in favour of Semmola's theory of hetero-albuminæmia is given by the late Dr. Cranstoun Charles in a paper on "Intermittent Albuminuria" (*St. Thomas's Hospital Reports*, vol. xxi.), and he mentions that in one young man he found, just as Semmola had done, some albumen in the perspiration and saliva, as well as in the urine.

The same author mentions several interesting cases of albuminuria associated with high blood pressure, mental depression or headache; one case in which there was albuminuria at the menstrual periods, and another case in which it was associated with constipation and relieved by blue pill and salines. I should have no doubt that the mercury and the salines affected the capillaries all over the body as well as the intestines. He also speaks of the effects of exposure to cold and its possible influence on the skin, and mentions several other points which are in favour of the metabolic origin of these albuminurias.

I have already said that the cases of albuminuria described by Dr. Dukes are associated with high blood pressure, influenced greatly by diet, and that he himself considers that they often pass on into Bright's disease.

I differ from him, however, in believing that such albuminuria and such Bright's disease are not due to hyperæmia of the kidneys, but are the result of a failure in metabolism and hetero-albuminæmia, which alone will explain all the facts of the case.

When the failure of metabolism is slight and the hetero-albuminæmia occasional, very slight change in diet, clothing, exercise, or climate, may suffice to remove it, as in some of the cases I have mentioned; but when it is more severe, and especially when owing to atrophy of metabolic structures it has become organic, or still more, if it is complicated by a kidney lesion, these measures will no longer remove the albumen, and complete cure may be impossible.

The kind of albumen excreted seems also to tell the same tale, for it is now pretty generally recognised that in functional cases as well as in paroxysmal hæmoglobinuria, the albumen in the urine is mostly globulin, which dialyses freely, while in advanced cases with probably distinct and definite kidney lesion, serum albumen is present, which will not dialyse (*Lancet*, 1889, vol. ii., p. 1806). Now, the late Professor Semmola pointed out many years ago that in early and acute cases there is an excess of diffusible albumen in the urine and in the blood; while in advanced cases with distinct kidney

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lesion, the albumen in the urine may be almost entirely serum albumen.

The serum albumen passes only when there is a kidney lesion; the diffusible albumen passes at any time, because it is diffusible. Its presence in the urine is a sign of hetero-albuminæmia, just as glycosuria is a sign of glycæmia.

Where diffusible albumen is alone present, the conditions are still functional, and diet treatment which removes the hetero-albuminæmia, may cure quickly and completely; but where serum albumen is passing, diet will no longer cure promptly, and may not cure at all, for the removal of the hetero-albuminæmia does not do away with the kidney lesion which is now present and allows the serum albumen to pass.

It has been pointed out that pyrogallic acid, toluylendiamin, &c., when used to produce hæmoglobinuria in animals do eventually bring about severe nephritis (*Lancet*, 1885, vol. i., p. 115).

Is it the substance itself, or its effects on the blood, that produce the nephritis? Semmola, at least, would probably have attributed a share of the result to hetero-albuminæmia and hæmoglobinæmia. The late Dr. Ralfe suggests (*Lancet*, 1886, vol. ii., p. 764) that functional albuminuria is but a minor degree of paroxysmal hæmoglobinuria; and I have pointed out that in both troubles there are often abundant signs and symptoms of collæmia; and this author himself points out, that in functional albuminuria there are frequently bilious attacks which I should translate by the one word collæmia (see above case of E. H.). He also says that arsenic diminishes the hæmolytic action of the liver, and strengthens the resisting power of the red cells; it did not appear to do so in the case of Daniel H. given above (p. 383); but there was severe collæmia, and treatment of this was followed by general improvement. Arsenic, as we shall see in chapter xvi. probably clears the blood of uric acid, and would no doubt in this way affect its quality, but it failed to clear the blood of uric acid in the case of Daniel H., because of its great alkalinity due to his feeble nutrition and therefore it did no good. Several writers have suggested that bile salts affect the hæmoglobin (MacMunn, *British Medical Journal*, 1888, vol. ii., p. 117; Oliver, *Lancet*, 1885, vol. i., p. 977). They may do so, but it seems to me that the known effects of uric acid give a better explanation of concomitant symptoms, and in many cases, as I have shown, there is evidence of collæmia.

But supposing that uric acid in the blood can thus bring about hetero-albuminæmia, albuminuria, and nephritis; the nephritis,

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when it has come into existence, will have an important effect on the excretion of uric acid; for anything in the nature of inflammation in the kidney must diminish its alkalinity; and if the alkalinity of the kidney is less than that of the blood and tissue fluids generally, it follows from my first principles (chapters ii. and iii.) that any uric acid that comes to the kidney will be rendered insoluble and retained, instead of being excreted, hence it comes about that though we have plenty (too much) of uric acid in the blood, we have too little in the urine in Bright's disease.

Hence it comes about that in acute nephritis (but not so much in very chronic disease), no matter what may be the alkalinity of the blood, we get a holding back and retention of uric acid in the body, because the diminished alkalinity of the kidney is unfavourable to its solubility and excretion.

Hence, in nephritis we have chronic collæmia and its signs, obstructed capillaries, high blood pressure, if the heart is a strong one, slow action of the heart (bradycardia), scanty urine, retention of water in the body and general dropsy, with other signs of collæmia, such as headache, mental depression, tendency to suicide, all of which are well-known to occur in Bright's disease.

An interesting case, illustrating some of these points, was admitted under the care of my colleague, Dr. Tooth, at the Metropolitan Hospital, and he very kindly gave me leave to mention it. A boy, 8 or 9 years old, admitted with subacute nephritis and general dropsy. Urine only 15 to 16 ozs. in twenty-four hours. Measles was accidentally introduced into the children's ward, and this patient, with others, took the disease. The effect was magical. As soon as the fever had reduced the blood-pressure, the urine ran up, and was for several days about 80 ozs. in the twenty-four hours, and in two or three days the dropsy had nearly all gone. Here the rise of temperature and concomitant rise of acidity cleared the blood of uric acid, freed the capillaries, among others those of the kidney; the result was a copious diuresis and removal of the dropsy. Now precisely the same can be done with drugs, acids, opium, mercury, any of those in chapter ii., mentioned as causing retention of uric acid, and the result will be proportional to their power over uric acid. In some cases of nephritis I have, with these drugs, altered the pulse rate from about 44 to 80 or above (see fig. 35, p. 167) at the same time reducing its tension, and with this went increase of urinary water, removal of dropsy, and diminution of albumen. Nature is, however, generally more powerful than any drugs, as the above case well illustrates; but

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I believe that she acts in the same way by clearing the blood of uric acid.

It may be asked, why, in chronic interstitial nephritis, while there is still high blood pressure, do you get no holding back of water and no dropsy?

I have suggested, as the result of my own observations on the matter, that in chronic nephritis the collæmia is greater in the alkaline tide of the morning, and, as a result, the pulse is slower, and the urine more scanty at this time. Later in the day—the evening and night—collæmia is less, the capillaries are relatively free, and a considerable diuresis makes up for the scanty excretion of the other hours. (See quantities of urine per hour in table given by Saundby, previous reference, p. 15.)

For a case in which this was so, see *Lancet*, 1890, vol. ii., p. 133. In this way there is no retention of water in the body in chronic Bright's disease, for though the capillaries are obstructed and the tension high, the heart is equal to its work, and especially at night the circulation is free. In acute Bright's disease, the sudden obstruction of capillaries may overpower the heart, and dropsy results. In all cases I believe it is a struggle between the heart and the obstructed capillaries; if the heart fails there is dropsy, if it wins there is none, (see Marey's observations, quoted in chapter v., p. 143).

If we wish to understand dropsy thoroughly we must study most carefully the relation between the excretion of uric acid and that of water in the physiology of every-day life; in the morning hours even in physiology there is more water in the blood and tissues than in the evening, and in the uric acid headache the water in the tissues often increases so as to be visible, and between this and dropsy, either cardic or renal, the difference is only one of degree: in cardiac dropsy the water fails to pass the kidney because the heart has lost the power necessary to pass the blood through the kidney vessels; in Bright's disease the heart's power is undiminished, but the kidney vessels are obstructed by uric acid.

In chronic nephritis, also, the alkalinity of the kidney is less reduced than in the acute disease, hence the holding back of uric acid and consequent collæmia is relatively less severe.

Collæmia is probably, therefore, more severe in sudden and acute cases, and this corresponds with the relation of uræmia, the poison of which is, I believe, in not a few cases, simply uric acid, and its symptoms, at least the most prominent ones, are the results of the action of this poison on the vessels, and so on the circulation of the brain.

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Before the attack, as is well known, the urine is often extremely scanty and the pulse may be as slow as 40 (intense uricacidæmia). The case in which I altered the pulse rate from 44 to upwards of 80 had slight convulsions, severe headache and other signs of uræmia at the time of admission under my care.

The very close parallel between the symptoms of uricacidæmia and those of uræmia has long interested me, and I believe that till a fatal lesion is produced, I have the same power over the one as the other. Let us look for a moment at the main symptoms of uræmia, and first, epileptiform convulsions. I have shown that similar convulsions may be the work of uric acid; then headache, giddiness, drowsiness, cold skin and cold sweats, local arterial spasms, "dead hand," vomiting, slow high tension pulse, scanty urine—why, these are all the signs of the uric acid headache (migraine). Amaurosis, again, is probably merely an exaggeration of the well-known eye symptoms of migraine.

I have obtained considerable quantities of uric acid from the blood of uræmic patients, as ·0025 per cent. from a case under the care of my colleague, Dr. Tooth, at the Metropolitan Hospital, and ·0021 from a case under the care of Dr. R. Kirk, of Glasgow, who kindly sent me the specimen, and ·0048 per cent. from a patient of my own at the Royal Hospital for Children and Women, who was 17 years of age, and had a large, pale kidney. Her temperature was 105° soon after the blood was drawn, and when a little later she came out of the coma she complained of a severe headache, in many respects resembling that of uric acid. In the first case the temperature was 103·8 at time of cupping, and the amount found was probably only a fraction of the quantity in the blood when the uræmic symptoms began; but even so, it is nearly four times as much as is found in other diseases associated with fever, as ·00067 per cent. in pneumonia with temperature 102°.

We have here, then, as I have shown, all the causes which produce collæmia; and all the signs of its presence and, further, all the drugs which do good in treatment (opium, acids, &c.), clear the blood of uric acid, while bleeding mechanically reduces the tension and pressure by means of which the uric acid fatally affects the nerve centres (see p. 200).

Thus in a case recently under my care I believe that I can trace all the factors that led up to a fatal uræmic convulsion.

Lydia M., aged 44, admitted into the Royal Hospital for Children and Women, on April 2, 1897, suffering from chronic Bright's disease, heart failure, and dropsy.

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On admission temperature 97°, pulse 80. High tension.

I saw her two days after admission and found that she had been put on pulv. jalapæ co., and a pill containing mercury, squill and digitalis, to be taken three times a day. Heart's apex beat fifth space, one inch outside the mid-clavicular line; the first sound was long or reduplicated, and the second sound loud and sharp both at the apex and base.

Her temperature had risen to normal, pulse 84, and the bowels were open two or three times every day.

Urine had sp. gr. 1012, and contained a considerable amount of albumen.

April 8 and 9 there were some teeth troubles, ending in stomatitis.

April 10, pill left off, and a mouth wash was given.

The pulse had gradually slowed down, no doubt owing to the digitalis and the rest in bed, to 72 on 7th, 66 on 8th, 60 on 9th, and 56 on 10th, and it now further slowed to 52 on 11th, and 42 on 12th April.

The first part of this slowing was no doubt due to the rest in bed and the digitalis, and with this improvement in heart power the dropsy had all cleared up.

On the 11th and 12th there was very marked stomatitis, and the pulse slowed still more to 52 and 42 in spite of the digitalis having been left off, and showed still higher tension.

I saw her for the last time on the afternoon of 12th, after the resident medical officer, Dr. Key, had noticed some twitching of the face.

The pulse was then regular and only 36 in the minute and showed very high blood pressure, and the patient was dull and inclined to be drowsy.

I concluded that she was suffering from severe collæmia as a rebound after the mercury, and ordered some iron and other drugs with a view to stop this and lower the blood pressure.

Before these had had any time to act however, at 6.30 p.m. the same evening she had a severe convulsion fit, in which she died.

Now these symptoms tell their own tale.

On admission she had collæmia with subnormal temperature and quick pulse (heart failure) and their result—dropsy.

A week's rest in bed, with the help of squill, digitalis and mercury restored the temporarily disabled heart, its rate of action slowed to normal, and the dropsy disappeared.

Then came the stomatitis, necessitating the stopping of the

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mercury, and the natural result was a post-mercurial collæmia or rebound.

But the heart was now fairly strong, and so the pulse got slower and slower as the pressure rose, and the high pressure in the skull produced first twitchings of face muscles, then drowsiness, and finally a convulsion which was fatal.

I now regret that I did not order her to be bled on the afternoon of the 12th, when things were clearly very threatening; but if she had survived the first convulsion, this treatment, the only one I expect much from in acute uræmia, would no doubt have been carried out.

I will now give a few notes of some of the more interesting cases of Bright's disease that have come under my care.

Charlotte W., age 15, admitted under my care at the Royal Hospital for Children and Women, October 28, 1890. She had been seen by my colleague, Dr. Wheaton, on October 22 at the Surrey Dispensary complaining of numbness and loss of power in the right hand and of "fainting fits."

On October 26 she was quite comatose for some time after a succession of convulsions.

On admission she was noticed to be quiet and drowsy and slow in answering questions. The face was pale and the eyelids puffy, and there was some œdema of the back and chest.

Pulse 66, high tension, with a well-marked W. tracing, as in fig. 35 A. Heart's apex outside left nipple line, first sound long (? systolic murmur), second sound very loud both at apex and base. Lungs, a few râles at both bases. Some little ascites. Urine 1025, some blood, and albumen 7 p. 1,000 (Esbach).

October 30 she was given pulv. jalapæ co., a hot air bath at night and some citrate of potash with a little nux vomica.

October 31.—Some headache this morning, but no fits since admission.

November 1.—Pulse, morning, 48; still some headache. Pulse, evening, 60. Heart, second sound still very loud.

November 3.—Pulse, morning, 48. Evening, 48.

November 6.—Pulse, morning, 50; evening, 44. Citrate of potash left off and salicylate of soda given after meals with acid mixture (nitro hydrochloric acid) before meals.

November 8.—She had a little diarrhœa, so all drugs were left off.

November 9.—Pulse, morning, 54; evening, 54.

November 10.—Salicylates and acids begun again yesterday. Pulse, morning, 60; evening, 60.

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November 15.—Pulse, morning, 72; evening, 72.

November 17.—Salicylates and acids left off. Pulse, morning, 72; evening, 86, and a tracing now showed comparatively little tension.

November 27.—Pulse rate had fallen again and was morning, 56; evening, 68. Soon after this she was allowed to get up and the pulse rate quickened in consequence.

The albumen, which was very high in the specimen on admission, was not much more than 1 per 1,000 in a 24 hours' specimen. On November 10 and 13 it was still 1·0 per 1,000, but on the 17th it was ·5 per 1,000, and it remained at or about this amount during the rest of her stay, with the exception of the 24th, when it was ·6 per 1,000.

The urine at first contained fairly numerous casts, hyaline with granules and degenerate epithelium.

She was given fish on November 27, and she went on well, having no fits, no headache and no increase of albumen, and she was allowed to go home on December 5.

This case seems to show, as does also one previously mentioned in chapter v., that citrate of potash neither quickened the pulse nor lowered its tension, while salicylate of soda and acids did both very decidedly, though it tended to slow down again after these drugs were left off; and the most decided fall of albumen coincided with their action and the lowered blood pressure they produced.

Alice M., age 8. Admitted into the Metropolitan Hospital under my care December 4, 1891.

December 5.—Pulse, morning, 68. Tracing shows very high tension, predicrotic wave rising above the upstroke. Urine, 18 ozs., 1018. Albumen, ·5 per 1,000 (Esbach). Fairly numerous hyaline and granular casts. Given acid and salicylate mixtures as in the previous case.

December 9.—Much better in self. Pulse, 84, and first wave is now well below the upstroke. Urine, 24 ozs., albumen, little more than a trace.

After this albumen remained about a trace only, and she went home at the beginning of January.

All drugs were left off on December 23, and the pulse on December 27 had fallen to 58.

Ada P., age 16. Admitted under my care in the Royal Hospital for Children and Women on November 23, 1893.

She had recently recovered from scarlet fever. Urine, 40 ozs. in 24 hours, containing 2·0 per 1,000 of albumen (Esbach).

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Casts very numerous, large hyaline and granular, some fatty and some epithelial.

She was put on iodide of potassium and nux vomica, and was given hot air baths frequently, and aloes and iron pills for the bowels occasionally.

The urine became alkaline, the temperature remained subnormal, and she remained for a long time without much improvement or decided decrease of albumen.

After she had been in for more than two months, it struck me that the hot air baths were really doing harm, causing weakness and depression, alkaline urine, increased alkalinity of the blood (see fig. 63 as to the effect of a Turkish bath), and subnormal temperature; that, in a word, instead of increasing the combustion and metabolism of the body, we were diminishing it.

They were accordingly reduced and left off, and with this the temperature rose to normal or slightly above it, and remained there till she went out in February. With this she improved more decidedly, and the albumen was reduced to a trace when she left.

Her case left on my mind the impression that the hot air baths did harm, and that if we had left them entirely alone and trusted to drugs, such as the iodide of mercury, which clear the blood of uric acid, we should have got rid of her albumen much sooner.

In any similar case in future, I shall take the temperature as my guide, and refuse to believe that any treatment is doing good and increasing the metabolism of the body while the temperature remains subnormal; and, indeed, it is an important characteristic of the best action of the iodide of mercury in these cases that as the pulse softens and quickens, the temperature rises to normal and remains there.

Isabel M., age 46. Admitted under my care into the Royal Hospital for Children and Women on June 14, 1894.

She complained of general œdema and shortness of breath with occipital headache.

Her temperature was 102° and her pulse 78 in the evening and 60 in the morning, being thus very slow relatively to the temperature. A tracing showed a very high first wave, and took 4½ ozs. pressure to devolop it.

The heart's apex was displaced to the left beyond the nipple line, its impulse was forcible and the second sound everywhere loud.

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There was some twitching of the arms.

Urine 1020, and contained albumen and blood.

She was put on milk diet, iodide of potassium and nux vomica.

June 18.—Urine 89 ozs., albumen 2·0 per 1,000 (Esbach) and a little blood. A few large hyaline casts with epithelium granules and fat upon them.

Pulse 84, temperature 99·6°. Still some occipital headache, with nausea and occasional vomiting.

Hst. hydrarg. perchlor. cum. pot. iod. given in place of the other iodide mixture.

June 28.—Urine 54 ozs. (there is little or no œdema left, *i.e.*, there is no more water to be run out of the tissues and blood) sp. gr. 1010 acid.

Temperature, 99°. Pulse, 90.

There were now some signs of salivation, so I cut off the mercury and put on the iodide of potassium again.

July 5.—Urine, 50 ozs., sp. gr. 1010. Alb. (Esbach) ·5 per 1,000.

July 7.—Pulse, 80-90, much lower tension and only 3½ ozs. pressure is now required to develop the tracing.

July 17.—Urine, 61 ozs., 1010 acid albumen only a trace.

No symptoms.

July 18.—Allowed to go home and given the iodide of potassium mixture to continue.

I concluded that her troubles on admission were due to uræmia, and that we drove it off by clearing her blood of uric acid, relaxing her pulse and freeing her metabolism, so that her albumens were combusted, and not eliminated unchanged.

Lily T., age 5. Admitted into the Royal Hospital for Children and Women, February 23, 1894.

She had general anasarca, her face was pale and puffy, and there was a history of scarlet fever two years ago.

Pulse, 60, high tension. Temperature, 99·2°.

First sound of heart long or reduplicated; second sound loud.

Urine, 20 ozs., smoky, 1018.

Albumen (Esbach)	2 per 1,000	= 18·4 grs.
Urea	1·4 per cent.	= 129 ,,
Uric acid	·04032 per cent.	= 3·7 ,,
Relation of albumen to urea		1—7.
,, uric acid to urea		1—35.

Casts numerous with much epithelium.

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Here we have subacute Bright's disease with, no doubt, a large amount of uric acid in the blood, accounting for the slow high tension pulse, but no large excretion in the urine owing to the irritation in the kidney interfering with its solubility and preventing its passing, as it usually does in physiological conditions, from the blood into the urine.

And with this we have scanty urine, low urea = 3·7 grs. per pound, her weight being 34lbs. and a considerable excretion of albumen equal to 1 grain for 7 of urea; and with the cold pale skin and anasarca, we have every sign of obstructed capillaries and consequent diminished combustion and its results.

She was put on the mist. hydrarg. perchlor., cum pot. iod. and milk as her only food.

She went on well and on *March* 2, her urine was 50 ozs., sp. gr. 1020, containing 1·5 per cent. of urea = 375 grs.

Albumen a mere trace, too small to estimate.

Temperature normal. Pulse 120, soft.

Second sound of heart still loud, but the first sound is not long.

Surface warm.

Here was indeed a different state of things all in one week.

Her urea had increased to 11 grains per pound and the albumen had diminished to such an extent that it could not be accurately estimated, while her diet had not been altered.

March 19.—Urine 18 ozs.; there was no anasarca.

Urea	1·8 per cent.	= 149 grs.
Albumen... ...	·5 per 1000 (Esbach)	= 4·1 ,,
Albumen to urea...		1—36.

April 7.—Is now up and about—

Urine 26 ozs., sp. gr. 1020 acid.

Albumen too small to estimate, say ·25 per 1000 = 3 grs.

Urea 2·2 per cent. = 263 grs. = 7 grains per pound.

Relation of albumen to urea 1—87.

She was now on milk diet. She went on perfectly well and was allowed to go home.

I have no doubt that if she went on well and had no accidents such as over-feeding, or exposure to cold, the albumen would in 8 to 10 months have completely disappeared and that no one who then examined her urine would ever guess that she had had Bright's disease.

With regard to the large excretion of urea on March 2, we can now see from the experience we have had with the effects of uric

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acid on metabolism, and especially its effects on the causation of fatigue and the excretion of urea during and after exercise (figs. 39 and 40), that this excretion was to some extent a measure of her previous defective metabolism.

It was not due to any increase of food or to better assimilation of food, for food and assimilation continued the same and yet the high urea did not last, and on April 7 urea was 7 grs. per pound as against 11 grs. per pound on March 2.

It is clear to my mind, therefore, that this high urea about March 2 was the result of her previous collæmia and defective metabolism of which, as I say, it was a measure, and represented the wet blanket of imperfectly metabolised nitrogen, which was accumulating in her muscles and other tissues, while their circulation was obstructed by uric acid.

But as soon as the blood was cleared of uric acid her circulation was set free, combustion became more complete, and the large excretion of urea represented the products of the previous incomplete metabolism which, owing to defective circulation, were left in the interstices of her tissues.

Here we have merely an enlarged edition of what we have already seen to occur in the physiology of fatigue where the collæmia produced by heat and perspiration obstructs the capillaries and reduces metabolism, causing an immediate fall of urea; then later on when the circulation has again become free we get a rise of urea which more than compensates for the fall of the previous day. (See figs. 39 and 40, and p. 284.)

In both conditions, fatigue as well as Bright's disease, we have only to get rid of the collæmia to get a free circulation and metabolism and a complete reversal of all the effects of the obstructed circulation.

With regard to the future of such cases, I will now shortly mention the after history of another case, Susan B., age 13, who was treated in the same way as some of the above cases, and like them discharged at the end of some two months with the albumen reduced to a mere trace, and has continued to attend as an outpatient ever since.

I first saw her on January 19, 1891, and she left the hospital for a convalescent home on April 4.

Her mother seemed to be a sensible woman, and I impressed upon her the great importance of giving her no animal food except milk, of clothing her in flannel from head to foot, and as far as possible guarding against exposure to cold and wet.

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She came to see me about once a month, and in October, 1891, I have a note that at this and the previous visit I was unable to detect any albumen in the specimen brought.

In 1892, this improvement continued, and she was now growing a strong and healthy looking young woman.

In 1893, she had during some cold and wet weather, a slight relapse, and there was a trace of albumen in the specimen brought, and she had not been feeling quite so well and looked a little puffy again.

Bear in mind here the direct effect of cold on the circulation of the skin and also its indirect effects through precipitating collæmia.

But I put her on iodides and she soon got all right again and the urine remained free from albumen as before.

In 1894 this condition continued and I again began to regard her as completely cured, provided she kept to diet and regulations.

In the spring of 1895, however, she returned with some albuminuria and had also some *malaise* and the general signs of collæmia and defective combustion.

And this time she had to confess that she had been doing wrong, she had been doing some work, and what was much worse, had been eating some meat.

This was a great disappointment to me as I had began to look upon her as cured; but after all it is nothing more than what would have occurred if her trouble had been migraine instead of morbus Brightii; in both diseases immunity depends upon a steady continuation of the diet, the moment the introduction of uric acid is increased the trouble returns. If she had been content with her milk diet she could have worked as hard as most other people without any harm; but she went out to work, and was, I fear, practically compelled by circumstances to eat meat as others did.

I have again seen her more recently; she has been keeping strictly to diet, refusing to indulge even on Christmas Day. Her appearance does the diet every credit, and the urine is quite free from albumen, and has sp. gr. of 1017.

I have since seen this patient several times in 1896 and 1897. She now keeps faithfully to the diet: there has never again been any albumen in the urine, and the sp. gr. runs from 1015 to 1020, and collæmia being impossible, cold weather has been unable to affect her.

In a case under my care, a patient suffering from chronic arthritis and periostitis (believed by Mr. Walsham, who saw him

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with me, to be rheumatic), and also from parenchymatous nephritis, I was interested to find that both troubles fluctuated together; that when he had increased trouble in his joint he also had increase of albumen or even recurrence of blood in his urine, so that it looked almost as if the condition (? rise of acidity) which drove the uric acid into and produced increased irritation of his joint, had driven some also into the kidney (gout of the kidney) and increased the renal trouble, and I think we must not altogether lose sight of this possibility; but, on the other hand, it is clear that any arthritis which is due to uric acid is due to a fluctuation of uric acid—that is, there is first an excess of uric acid in the blood (uricacidæmia) and then some rise of acidity precipitates it on the joint (see chapters xv. and xvi.), and though both troubles appeared to get worse together the increase of albumen may have been due to the collæmia in the way I have suggested and not to the local irritant action of uric acid in the kidney.

I was greatly interested in this case because, when I put him on a milk diet, both his arthritis and nephritis steadily improved together, and he was greatly pleased with the result of this treatment. I have no doubt that both were due to uric acid, the action being direct in the arthritis, probably indirect in the nephritis.

Another case somewhat similar to those given is that of Edwin R., aged 52, admitted into the Metropolitan Hospital under my care, April 1, 1896, suffering from swelling of the legs and headache for two weeks. There was a history of some kidney trouble on and off for about six years.

On admission the face was puffy and there was some œdema of the legs.

Temperature subnormal. Pulse 90. Heart's apex beat well outside the left nipple line. Impulse diffused and heaving.

April 4.—Urine full amber, pale deposit, 1020 acid, quantity 30—48 oz. per day.

Urea 2·2 per cent. Albumen (Esbach) 1·5 per 1000. Relation 1—14.

Microscopic examination of deposit. Numerous casts. Hyaline with granules degenerate epithelium and fat.

Pulse rate 100. Diameter of R. radial artery with arteriometer while lying down = 2·2 mm. On milk diet. Given mist. hydrarg. perchlor. $\bar{c}$. pot. iod. ter.

April 8.—One pint of milk added. Mixture to be taken *quater in die*. R. radial diameter 2·2 mm. Pulse rate 112.

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April 11.—Urine shows some slight increase in quantity.

Blood examined at 4 p.m.:—

$$\frac{\text{Hæmoglobin}}{\text{Cells}} = \frac{\text{60 per cent.}}{\text{106 per cent.}} = \text{blood decimal} = \cdot 56.$$

April 13.—Urine 68 oz.

April 16.—Urine 72 oz., 1014 acid.

Urea 1·3 per cent.
Albumen ·3 per 1000 } 1—43.
R. radial diameter 1·7 mm.

April 20.—R. radial diameter 1·7 mm. Albumen is now reduced to a trace too small to be estimated.

April 28.—Up and about in the ward.

Blood to-day:—

$$\frac{\text{Hæmoglobin}}{\text{Cells}} = \frac{65}{103} = \cdot 63.$$

Here as the result of three weeks and three days on iodide of mercury and diet, we have the urine increased and the dropsy removed; the blood pressure lowered, as shown by the fall in the diameter of the radial artery, the capillaries freed and combustion stimulated, as shown by the fall of albumen which was reduced from a relation to urea of 1 to 14, down to something less than 1 to 43, and lastly we have a very distinct improvement in the quality of the blood itself produced here, just as in chlorosis and by the very same drug (see fig. 49), showing conclusively that all the above results of the removal of collæmia by iodide of mercury were due to a general improvement of nutrition and metabolism. But after all said and done this is but the same effect on a larger scale as can be produced any day and in any one in the physiology of fatigue.

This patient continued to do well and the iodide o mercury mixture was now only given three times a day. He was put on a uric acid free diet containing milk, and cheese with bread, puddings and farinaceous dishes *ad lib.*, also vegetables and fruit, and once a day some pease-pudding or other pulses. When he was sufficiently instructed in this diet he was allowed to go home, still continuing the mixture, which was later on changed for one containing iodide of sodium and nux vomica, which he kept on with together with the diet for a long time.

November, 1896.—Is keeping faithfully to the diet, which he likes, and is very much pleased with the improved health he has gained. I have examined several specimens of urine lately and have found no trace of albumen in any of them.

Here as in other cases there was a comparatively quick reduction

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of albumen at first, as it fell to a trace in the third week of treatment; but that trace remained for several months more only gradually diminishing and becoming invisible. This, I think, shows the two origins of albumen in such a case; the larger amount, which disappeared at once, was the albumen of defective combustion which was at once metabolised into urea as soon as the capillaries were cleared and the fire burnt up; the small lingering trace was the organic albuminuria, the measure of the injury done to the kidney, and possibly as the late Professor Semmola suggests, to the blood albumens themselves by the experiences they had passed through, and these injuries take some time to repair and pass away.

If all cases of Bright's disease were like those just narrated, and if in all cases the iodide of mercury acted just as it did in these, I should have little or no doubt of my power to cure every case of Bright's disease that came before me; but as this is unfortunately not the case, I must not forget to mention the other side of the picture—the cases in which I fail, and the reasons of such failure.

Of course if mercury disagrees, if it causes salivation, dyspepsia, or diarrhœa, as I have already pointed out, it quite fails to control uric acid collæmia, and is worse than useless in the diseases which are due to it, and iodides also may cause iodism and have to be left off for this reason; and unfortunately in not a few cases we are deprived of the use of these most powerful drugs by such results.

In this case we should remember the effects of salicylates with acids, or salicylates with opium in small doses, for though less powerful than iodide of mercury, they may chance to succeed.

But even when the iodide of mercury does not cause salivation or upset the stomach and intestines, it may fail to cure, and that for a reason which will be best illustrated by a record of a case in which it twice succeeded, and then in a second relapse failed to reduce the albumen at all.

Edgar G., aged 18, first admitted under my care into the Metropolitan Hospital on September 18, 1895. There was a history of Bright's disease extending over more than two years.

He had now considerable general anasarca, and some ascites, and the urine contained nearly 7 to 8 per 1000 of albumen.

He was given iodide of sodium with some nux vomica and occasional small doses of calomel, but he did not improve much.

October 20.—Abdomen tapped and 7½ pints of fluid withdrawn.

October 23.—Given mist hyd. perchlor. c. pot. iod. with nux vom. and digitalis. Pulse 92. Temperature subnormal.

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October 25.—Abdomen again tapped and 8½ pints withdrawn. Pulse 104.

October 27.—Temperature rising towards normal. Urine increasing. Pulse 92, and this was the beginning of a very marked improvement, the iodide of mercury coming into action, and being aided by the nux vom. and digitalis, and last but not least, by the tapping and removal of ascites.

November 1.—Much better; œdema all gone; is passing 40—70 oz. urine. Pulse 88.

November 19.—Pulse 88; urine 66 ozs.; sp. gr. 1011; neutral albumen ·1 per 1000; urea 1·1 per cent.; relation 1—91; allowed to get up.

December 5. — Left hospital; albumen a mere trace; urine plentiful; advised to keep always on milk diet.

May 20, 1896.—Re-admitted with a relapse; had been at work as a stable boy, and was not able to get proper food; temperature subnormal (sign of defective combustion); general anasarca and slight ascites as before.

May 22.—Urine 16 ozs.; amber turbid, 1024, acid.

Albumen (Esbach) ·625 % = 46·2 grs.
Urea ... 3·7 % = 279 grs. } 1—6.

Microscope shows very numerous casts; much degenerate epithelium and fat; very different from the urine when he went out in December last.

He again improved on the same iodide of mercury mixture with nux and digitalis, and after the ascites had been tapped once or twice, but he did not respond to the drugs so quickly as on the previous occasion, and there were evidences of increasing cardiac dilatation and quickening of the pulse.

However, by June 13, and especially after a paracentesis abdominis on June 1, the urine increased to 48, 56, and 60 ozs., and began to contain little more than a trace of albumen, giving a relation to urea of 1—25 and less.

After this the amount of albumen became so small that it could not be estimated, and the urine at the beginning of July went up to 98 and 106 ozs.

He now again went out having received full directions and cautions as to the importance of diet; but this time he was too weak to work, and being dependent on others he had more than ever to take what food he could get, and then he was sent to a convalescent home and fed on soup, fish, meat, and what is generally called the fat of the land.

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He did not improve on it, however, but soon again got ascites and anasarca and was confined to bed, and then he got some sloughing sores on his legs, when an attempt was made to run off the fluid from the skin with tubes; and then he thought of me, and finally was again sent back from this convalescent home to the hospital to be under my care once more.

But this time I could do nothing for him, though a more suitable diet did some good, and the sores on his legs healed; but the drugs that had been useful before now quite failed either to increase the urine or diminish the albumen, and even repeated tappings failed to give them a start, and he remains like a marsh, full of water, and the water ever slowly rising and rising putting out more and more completely the fires of combustion.

And the explanation of this is fairly simple if we look upon Bright's disease as a failure of combustion, which again is due to defective circulation, which in its turn is the result of collæmia overpowering say a normal heart (acute Bright's disease), or as in this case a heart which grew gradually weaker and weaker as the general strength and nutrition failed.

And it is obvious that with a given amount of collæmia we shall get ever greater and more disastrous effects on the circulation, nutrition, and metabolism of the body, as the nutrition and power of the heart fail.

Then the scanty urine is a measure of the obstruction to the circulation in the vessels of the kidneys, and this is an index of the larger and more important obstruction to the circulation in all the great metabolic tissues of the body, which is the cause of the defective combustion.

Now there can be very little doubt that something of this kind happened in the case of Edgar G. With his first attack his trouble was almost entirely functional, a defective combustion due to acute collæmia. His heart was strong and well nourished, his tissues were young and moderately well formed and sound, and as soon as the collæmia was cleared up by drugs circulation and combustion were resumed, and he was soon again in a position to deal with all the albumens in his food. Hence urea increased, and albumen in the urine diminished till only a trace was left, and that trace was due to some little irritation in a few cells of the kidney, resulting from the passage of the albumen, while certain cells in the liver, skin, &c., had suffered a corresponding irritation and were also slowly undergoing regeneration.

But with these slight exceptions he was a sound man, and had

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only to make further collæmia impossible, by living on a uric acid free diet, to remain well and strong and be as in the previously mentioned cases, completely cured of his disease.

Unfortunately, however, he was unable to control his diet, so that collæmia, in place of being rendered impossible, was allowed to return, and he was once more subjected to a severe attack of defective combustion, with further damage to blood metabolic tissues and kidneys.

And thus we find that with each attack he recovered more slowly and with greater difficulty; in his first attack a mere clearing up of the collæmia by iodide of mercury would have sufficed to free the capillaries of the kidneys and run off the water, the fires would at once burn up, and the albumen be quickly reduced to a trace.

At the next attack, nutrition is not quite so good, and defective nutrition means defective power of muscle, especially of that most important muscle the heart, hence something more must now be done besides clearing up the collæmia, and nux vomica has now to be added to strengthen the heart in this attack; also there is now a slight but quite distinct falling off in the nutrition of the kidneys and metabolic tissues.

Nevertheless, he again becomes solvent and can again metabolise completely all the albumens of his food, and has once more a chance of life if he can control his diet.

At the next attack, however, things are still worse, and now both digitalis and nux vomica are required to get the heart up to its work; but the fires burn lower, the water rises higher, and the difficulty which the drugs meet with in clearing up the collæmia is greater owing to the increasing defectiveness of nutrition.

And so the issue is for some days in doubt whether the heart will get sufficient power to drive blood through the kidneys even when the collæmia has been removed; if it fails to do so the water will rise ever higher and higher, and the fires will soon be extinguished. And under these circumstances comparatively small matters suffice to turn the scale one way or the other, either for the heart or against it.

And one of these is no doubt the presence of a little fluid in the great serous cavities, the pleura or the peritoneum, and these by hampering the function of the lungs, the heart, the diaphragm, or otherwise impeding the circulation in the great digestive viscera, the liver, the kidneys, and the great abdominal vessels, may turn the scale against the heart and lead to its further dilatation, failure, and final defeat.

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Hence we see that the last time the iodide of mercury succeeded in the case of Edgar G., it only did so with difficulty and after every help had been given it by clearing the fluid out of the peritoneum; and I have had several hard fought cases in which fluid in one or both pleura had to be removed in the same way; but each time the effect became less and less, the fires burnt lower and lower as the metabolic tissues wasted, and the water rose in them ever higher and higher, and the heart muscle got weaker and weaker and less well nourished.

This is the final and absolutely hopeless stage of all Bright's disease: now it is little use to clear up the collæmia, for the nutrition of the heart is so bad it could not keep up a proper circulation, even if there was no collæmia; and circulation being so bad, the fluid is not run off by the kidneys, and the tissues of the body are like a marsh with great stagnant pools in the serous cavities, and the water and the collæmia between them now quickly extinguish the flickering flame of combustion.

But if this is the common and final ending of ordinary Bright's disease, and if as I said above, collæmia will produce more and more severe results in proportion as it supervenes upon an otherwise more and more defective circulation, then it follows that a collæmia, which would not of itself suffice to produce Bright's disease, may yet produce it if it chances to supervene upon either a condition of weakness or debility of the cardiac muscle, or on the other hand on a mechanical condition which more or less seriously obstructs the general circulation.

I think, therefore, that it is extremely probable that some people suffer from Bright's disease not because they have more severe collæmia than those others who do not suffer, but because they have rather weaker hearts, or more obstructed circulation, which allows the collæmia to do greater damage to nutrition and combustion than it would in an individual with a normal circulation.

Now the special condition I have in my mind's eye in making these remarks is that of pregnancy, for here we have, especially in primiparæ, a condition affecting the pressure relations in the abdomen, affecting the work of the diaphragm, the circulation in the great digestive viscera, and the great abdominal vessels, playing in fact, exactly the part of the ascites in the case of Edgar G.

And I find in Fagge's "Medicine," second edition, vol. ii., p. 624, the statement: "In women pregnancy is often the cause, as the late Dr. Lever showed many years ago, especially in primiparæ, and above all when there are twins."

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The bearing of primiparæ and of twins on the pressure relations of the abdomen are too obvious to need further remark, and it is also, I hope clear, as it follows from my first principles, that pregnancy is an enormous stimulus, especially in young women and primiparæ to the nitrogenous metabolism of the system, and this means both excessive formation and excessive retention of the uric acid in the body, that is provision of the material for a more or less severe collæmia in the future. And we already know from the relationship of pregnancy to headache, epilepsy, mental depression, Raynaud's disease, &c., as treated of in previous chapters, that normal pregnancy is accompanied by retention of uric acid and its clearance out of the blood.

But if the pregnancy is not normal, if there is dyspepsia, and still more if there is vomiting, then it follows also from my first principles, that the blood will become again a good solvent of uric acid and then some of the large formation of uric acid, or some that has been already retained before the vomiting began, will pass into solution in the blood and a more or less severe collæmia will result. Now vomiting is exactly one of those things which, I believe, may precipitate Bright's disease on pregnancy. And the following case will illustrate several of these points:—

Ellen G., age 24, admitted into the Metropolitan Hospital under my care on October 12, 1895, being then in the fourth month of her first pregnancy.

Her history showed that on September 28 hæmaturia had been noticed.

On October 1 she had several "fainting fits."

On October 6, suffered from pain in the left side.

On October 8, suffered from vomiting, which continued up to admission.

There was some anasarca and œdema of legs; pulse, 68; temperature, 98° to 100°, irregular; heart's apex outside left nipple line; abdomen, slightly distended; uterus, easily felt in hypogastrium; urine, 1014; alkaline, blood-stained.

Albumen (Esbach), ·4 %
Urea, ... ·9 % } or nearly 1 to 2.

Left radial artery measured with the arteriometer, 1·9 mm.

Put on iodide of mercury in small doses.

October 19.—Pulse, 72; left radial measures 1·7 mm.

October 23.—Pulse, 72; albumen to urea 1—4 in place of 1—2 as on admission.

October 24.—Iodide of mercury in full doses.

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October 25.—Pulse, 84; left radial 1·5 mm.

October 30.—Pulse, 96; left radial 1·3 mm.

November 8.—Heart's dulness has diminished and apex come into left nipple line.

November 16.—Pulse, 92; left radial 1·5 mm. There is some increased heart dulness, apex has gone again a little to the left and there is some increased œdema of the legs. Some digitalis given.

November 19.—Same condition; pulse 88; left radial measures 1·6 mm. Iodide of mercury further increased.

November 23.—Pulse 85; left radial 1·0.

November 30.—Pulse 72; left radial 1·0.

December 6.—Pulse 88; left radial 1·1. There is still considerable œdema of the legs.

I now came to the conclusion that the iodide had twice cleared up the collæmia and freed the capillaries on October 30 and November 23, but on neither occasion had this been followed by diuresis and removal of fluid, and similarly combustion remained defective and albuminuria profuse.

The inference seemed to be that the increasing abdominal pressure, and the increased work that pregnancy, now in the sixth month, was throwing on the heart, prevented it reacting to the removal of the collæmia. I therefore gave up the attempt to do anything with drugs and trusted to nature with uric acid free diet and rest.

I have no doubt whatever that if we could have cleared out the abdomen the iodide of mercury would very quickly have improved the combustion and reduced the albumen to a trace; and the question of terminating the pregnancy was carefully considered with my colleague, Dr. Gow, but put on one side as being on the whole more dangerous than trusting to nature.

I could not but feel, however, that while we were thus waiting, the kidneys and great metabolic tissues were suffering serious damage, how serious it was difficult to say, but I knew from previous experience that such cases kept carefully on milk often got over parturition quite well, and that the Bright's disease then subsided to a greater extent than might have been expected.

Accordingly she was now watched for some months, during which the conditions remained much as before, the pulse ran about 80, and the radial artery measured from 1·7 to 1·9 mm. Urine scanty, loaded with albumen and a little blood.

In February, 1896, after reading the most interesting lectures of Dr. Handfield Jones, "The Heart, in its relation to Pregnancy,

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Parturition, and the Puerperal State," (*Lancet*, 1896, vol. i.) to which I shall have to refer again, I made a further careful examination of the heart and came to the conclusion that the quick pulse rate with a long and indistinct first sound, and a loud second sound both at apex and base, with increased dulness and apex displacement to the left, meant some heart failure before collæmia and the increased work and pressure in the abdomen, and I accordingly put her on a mixture containing phosphoric acid and strychnia, and it appeared to do some little good, for the pulse on February 25 had fallen to 72, and the left radial diameter to 1·6 mm., and the urine had increased somewhat to 46 ozs. per day, but still there was as before no practical result as regards the removal of anasarca and improvement of combustion.

On March 14, I examined the blood and found

Hæmoglobin 33 %
Cells ... 70 % } = Blood decimal ·47.

No doubt a very dilute and watery blood owing to the great retention of fluids in the body.

And so things went on without any material change up to April 21, when she was delivered of a full time living child after a fairly normal labour, and the fœtal heart had been heard and watched for several months past.

The temperature was slightly raised after parturition, and the urine began at once to increase reaching 113 ozs. on the day after it.

April 24.—Urine 80 ozs. General anasarca and œdema of legs decidedly less.

May 13.—Temperature now becoming normal after uterine inflammatory troubles, but is weak after them.

Pulse 80 to 90; left radial diameter 1·0 mm., albumen only ·05 per cent. now.

May 23.—Being now again under my care she was put back on the mixture of phosphoric acid and strychnia, and the pulse improved and slowed somewhat.

She remained weak and anæmic, but having been in hospital a long time she wished to go home, and was allowed to do so, continuing the mixture and the uric acid free diet.

July 16.—Saw her again; there is still a considerable amount of albumen, but she does not wish to come in for treatment with the iodide of mercury.

Her uterine troubles were unfortunate, for though no doubt the fever helped with clearing up the collæmia, appetite and digestion were much upset by them, hence nutrition and combustion remained

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poor, and the heart did not gain in strength as it otherwise might have done.

This case might, I think, be shortly summed up as follows :—

(1) Early first pregnancy, stimulated nutrition, retention of uric acid.

(2) Some upset or abdominal pain causing nausea and dyspepsia.

(3) Severe collæmia causing high blood pressure, albuminuria and hæmaturia, in fact, acute Bright's disease.

(4) Heart failure before the high blood pressure with "fainting fits."

(5) Vomiting either with the "fainting fits," a symptom of uræmia, or an exaggeration of the previous nausea and dyspepsia.

(6) Continuation of collæmia, high blood pressure and defective combustion, the latter being increased by the heart failure, which again was intensified by the increasing work and increasing abdominal pressure of advancing pregnancy.

(7) Collæmia partly cleared up by drugs; but the heart is still too much hampered to respond with a free capillary circulation and so combustion remains defective, and albuminuria continues.

(8) Great relief to heart and circulation at termination of pregnancy, but unfortunately digestion and nutrition are still held down, and so though the water increases and the albumen diminishes, the heart remains weak and nutrition and combustion defective.

(9) Result. Prolonged cardiac weakness, debility, collæmia and anæmia, prolonged defective combustion and permanent damage to kidneys and great metabolic tissues.

Prognosis very bad for future pregnancies, unless the heart and tissues are allowed a long time to recover; and doubtful or bad even as regards the continuance of life itself.

It has often been remarked that a woman may suffer severely in her first pregnancy, but if she gets over it well (better, I fear, that must be than Mrs. G. did) she may suffer little, if at all, in subsequent pregnancies, and this is no doubt due partly to the fact that the abdominal walls are now lax and the pressure and derangement of the abdominal circulation are consequently less than in the first pregnancy; but it is also, no doubt, partly due to the important fact that the heart has had time to hypertrophy and get level with the increased work, and so in subsequent pregnancies the defective combustion is never so severe (even if the collæmia is the same) as in the first pregnancy; and Dr. Jones (prev. ref.) tells us that in women who have had many children the heart remains permanently hypertrophied.

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I was greatly interested and instructed by reading the lectures of Dr. Jones while this case was under my care, as he points out that it has been shown that normal pregnancy causes hypertrophy of the left ventricle, and enlargement of the whole heart; and also that some cardiac failure from defect of this hypertrophy is by no means an uncommon cause of the signs of heart weakness in pregnancy.

He also points out most clearly the effects of the abdominal pressure of pregnancy in increasing the work of the heart, and shows that similar heart failure may also be produced by abdominal tumours. He further suggests that a previous pericarditis may in some cases explain the failure of the heart to get level with its work in pregnancy.

He also points out that the heart may not only fail during pregnancy but it also fails, perhaps more often does so, in the week after labour; and we must not, I think, here lose sight of the existence of post-puerperal collæmia and its possible effects on the heart and circulation.

Dr. Jones points out that this is by some believed to be due to some little fatty degeneration of the heart muscle taking place towards the end of pregnancy; but I cannot help thinking that this is a bit of doubtful physiology and pathology, and that the large excretion of uric acid (which is certain to follow the termination of a normal pregnancy, fed on ordinary meat food—post-puerperal collæmia) which as we have seen probably accounts for the greatly increased danger of giving chloroform at this time (chapter viii., p. 297) also accounts for the frequency of heart failure apart from chloroform, and one of Dr. Jones' cases of death after delivery greatly resembles in its symptoms post-chloroformal syncope.

The drugs that Dr. Jones finds useful in these cases are iron, strychnia, digitalis and nitrite of amyl.

If I may draw, in passing, one practical conclusion from these facts and observations it would be that all women who have the least sign of cardiac defect or debility should be kept throughout pregnancy on a uric acid free diet, to prevent as far as possible, the addition of collæmia to these other heart difficulties, either during or at the end of pregnancy.

And indeed, I think that all pregnant women might with advantage be kept on such diet, for even if by means of digitalis, strychnia, etc., you can prevent the heart from failing, that does not in presence of collæmia make combustion really good, and as shown by the very high arteriometer measurements in the case of Mrs. G., the arterial system is subjected to very great pressure and strain.

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There is not the least doubt that pregnant women can live on a uric acid free diet, for I have conducted not a few of them safely through it on an almost absolute milk diet, and we see by the quotations already given on pp. 222 and 287 that they can often do so with enormous advantage and relief from the very circulation troubles, high blood pressure, and general congestion of which I was just speaking; even if we may not throw in a greatly diminished chance of acute Bright's disease, and this last consideration would specially mark the value of such diet in primiparæ.

I would suggest also while these cases are fresh in our minds that heart failure, in other conditions than those met with in pregnant women, may allow of the production of seriously defective combustion (Bright's disease), by a collæmia that would not by itself have sufficed to produce it, and that in fact heart failure is an important contributing cause of such failure of combustion; the bad prognosis of heart failure in Bright's disease is well known, but this heart failure may have actually preceded the defective combustion, and been one of its causes. Hence the relation of Bright's disease to fevers may be a double one, first to the post-febrile collæmia already mentioned, and second to the weakened and debilitated heart muscle which so many fevers also leave behind them.

If the collæmia is slight and the heart strong there will be merely a temporary bradycardia with subnormal temperature as the sign of defective combustion; but if the collæmia is severe, and especially if the heart muscle is also weak, we shall have more decided and prolonged interference with combustion, shown not only in subnormal temperature with a quick and often irregular pulse, but with varying degrees of albuminuria and diminished urea up to what we have been accustomed to call undoubted Bright's disease; so that every post-febrile and collæmic bradycardia is Bright's disease in epitome, and differs from it merely in degree. Thus acute Bright's disease may be not only acute collæmia, but acute collæmia with its combustion effects intensified by a weak heart; and this weak heart will be either capable of improved nutrition and better work or not capable of these. If it is not capable the case goes rapidly to the bad, as there is no possible means of stopping the defective combustion, and as we have seen above even removing the collæmia may not be sufficient.

If on the other hand the heart has been only temporarily disabled and with removal of the mechanical cause of such disablement can attain to improved nutrition and power; combustion will improve somewhat, even in spite of the collæmia, and with improving com-

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bustion the collæmia itself will be diminished or cleared away; hence we shall get less defective combustion extending over a longer time (chronic Bright's disease).

But here again, also, there eventually comes a time when the nutrition of the heart muscle is so bad that satisfactory circulation and combustion are no longer possible, and then collæmia and hydræmia finally put out the fires.

We have here then standing out clear and plain the two conditions which in any given case of Bright's disease may render it impossible to cure by means of the iodide of mercury (1) the accidental evil effects of the drugs themselves on digestion and nutrition, and (2) heart failure.

I think, after a consideration of these cases and the effects that drugs produced in them, we can see pretty clearly the main points in the pathology and treatment of Bright's disease.

Bright's disease is but a name for the defective combustion of albuminous tissues and foods which defective circulation produces. And the cause of the defective circulation is uric acid present in colloid form and obstructing the capillaries.

The defective combustion is at first functional, and with the removal of its cause it soon comes to an end.

But after it has continued some time it produces atrophy of tissue, as shown, for instance, by Semmola in the case of the skin, and then combustion must always remain defective.

Within the limits imposed by this pathology we, having almost absolute power over uric acid, have also almost absolute power over circulation and combustion.

This pathology suffices to explain the relationship of Bright's disease to all other diseases, and also to diet, exercise, clothing, and climate.

Migraine with its slow high tension pulse, its low surface temperature, its falling urea, its increasing albuminuria, differs from Bright's disease in degree only; prolong it over days in place of hours and you have the full length picture of Bright's disease, and, as we have seen, the one only too often passes into the other.

Then, also, the treatment of the one is exactly the treatment of the other; clear the blood of uric acid and free the capillaries and you have cured either of them.

The treatment of migraine is to clear the blood of uric acid, and so order the diet as not to be continually introducing into the body an excess of it, and nothing more need be done for Bright's disease.

Any drug that clears the blood of uric acid will do what is re-

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quired, but if it fails to clear the blood it will be useless, and we have therefore to consider which drug is most likely to succeed under the conditions present in a given case.

The drugs I have used may not be the best, some other metal for instance, may have more power than mercury; and we want a clear understanding of their mode of action and not a mere blind following of a given prescription.

The pre-albuminuric stage of Mahomed is simply migraine and the functional troubles that accompany it, the headache being more or less marked according to the development of the anatomical factor (see chapter vi.). And the transition from this to Bright's disease is but the development of migraine into morbus Brightii, which can be seen almost every day.

The fall of urea at the onset of Bright's disease, upon which Semmola lays so much stress is, like the corresponding fall in fatigue, in migraine, or any temporary collæmia, a measure of the defective combustion which collæmia and obstructed capillaries produce.

If we can succeed in removing the collæmia we shall see a corresponding rise of urea just as occurs naturally the day after fatigue (figs. 39 and 40), or in Bright's disease, as shown in the case of Lily T. above given, and the same drugs will also prevent fatigue and the fall of urea that accompanies it (fig. 41).

The fact that the amount of albumen in the urine is absolutely proportional to the defective combustion but in no way dependent upon the kidney lesion accounts for the points so ably insisted upon by Semmola, and also for the fact that by controlling combustion we can often reduce the albumen to a mere trace in a week, while the kidney lesion, even if capable of repair at all, must obviously take a much longer time.

And, further, the effect we thus produce in pathology has its absolute counterpart in physiology, as we are there able to control the formation and excretion of urea from day to day and hour to hour by controlling the uric acid.

And in migraine with albuminuria, which comes between the two, we can prevent all trouble by a diet which prevents excess of uric acid from finding its way into the blood.

The relationship of Bright's disease to acute fevers is simply its relation to the defective combustion of post febrile collæmia; every fever causes retention of uric acid, as we saw demonstrated in a most interesting manner in the case of measles previously narrated (p. 446).

At the end of the fever there is a plus excretion of uric acid

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to a corresponding amount, producing as it passes through the blood obstructed capillaries and defective combustion to a corresponding extent.

I have also pointed out that in the case of other acute fevers there is not very rarely a temporary albuminuria on one or two of the days of subnormal temperature that immediately follow it; the subnormal temperature is a sign of deficient combustion, and the albumen when present is but another sign of the same thing.

It follows from this reasoning that the chance of albuminuria and nephritis following scarlet fever depends partly on the quantity of uric acid available for solution in the blood, and this in turn depends upon the diet both before and during the fever.

In this connection it would be of great interest to observe whether vegetarians[1] have immunity from these sequelæ, and my experience so far as it goes is decidedly in favour of this being the case.

The same fact explains also the well-known importance of an absolute milk diet during the course of the fever.

Several years ago I came across an observation made by Prof. von Jaksch in an article on kidney diseases in children,[2] which has seemed to me to be of immense interest from my point of view; for after naming a considerable number of drugs as practically useless he goes on to say that only with regard to one drug would he be inclined to make any exception, viz., salicylate of soda, for he has been decidedly impressed with the idea that cases of scarlet fever treated energetically and from the very beginning of the disease with salicyl preparations have not only had their dangers in general diminished, but have that specially dangerous complication, scarlatinal nephritis banished from their course.

If this observation should prove to be correct it would amount almost to a demonstration of my point, for if uric acid instead of being stored up during the fever is steadily eliminated by the action of salicylate as a solvent, there would obviously be little or none left to get into the blood at the end of the fever and produce collæmia and defective combustion, albuminuria and nephritis.

We have here, I think, an important indication for the treatment of many febrile diseases besides scarlet fever, though in all of them it would no doubt be a still greater advantage to have been on a uric acid-free diet for some years before their onset.

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[1] In making this observation it will be necessary to distinguish between vegetarians who eat eggs and drink tea and those who are on a uric acid-free diet. See chap. xvii.

[2] *Deutschen Medicinischen Wochenschrift*, 1888. Nos. 40 and 41.

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Before leaving these subjects, I must just mention a case narrated by Semmola,[1] because it illustrates several points I want to make as clear as possible. A woman, about the climacteric period, goes to see a medical man on account of feeling ill, and having a little skin eruption, he examines her water and finds sugar; he therefore puts her on a diabetic diet, but after some weeks she feels no better, and comes to Semmola, who finds that she has now no glycosuria, but an albuminuria in its place, and he thereupon makes the most instructive remark, that we are not dealing, either with diabetes, or with Bright's disease, but with a failure in combustion, *i.e.*, with a failure in the metabolic activity of the liver, skin, &c.; give such a patient excess of sugar, she would have glycosuria, or excess of albuminoids, albuminuria, and I shall have to mention an exactly parallel case in the next chapter, and for a case in which strict diabetic diet stopped glycosuria but produced albuminuria in a woman, æt. 64 (see *British Medical Journal*, 1896, vol. ii., p. 1443).

The relationship of Bright's disease to diet is simply its relationship to the amount of uric acid formed and introduced into the body by any diet, and which is available at some future time in the life history of that body for solution in the blood.

The more uric acid that is thus formed and introduced, the more certain is it that at some future time it will be in excess in the blood.

But if a man is killed, say by accident, in the prime of life, before his metabolism has begun to slacken, he may never have any excess in his blood at all, for the continual introduction of the stimulant uric acid keeps his blood clear, though it ever accumulates more and more in his body.

But beyond a certain point this stimulation and accumulation is no longer possible, for the machine is only wound up to go for a certain small number of years, even if the gradual accumulation of urates in various organs and tissues does not of itself suffice to clog the wheels and cause diminished efficiency in various functions; and then he will have a gradually increasing collæmia and all the worst results of defective metabolism including Bright's disease, will gradually make themselves evident, and this defective combustion will as we have seen, be precipitated or increased if he has also managed in some way or other to strain or weaken his heart.

But almost the same thing may occur to him much earlier in life if he gets an upset, such as a fever or a severe accident.

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[1] *Archives de Physiologie*, 1883.

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The fever causes a fluctuation in uric acid and the collæmia which follows it may so lower his nutrition that it gets down and is unable to rise, and then all his urate accumulations will come through his blood and ever further and further depress his combustion and lower his nutrition, and he soon finds that he has Bright's disease, diabetes or other chronic condition of deficient combustion (see chapter iv.).

Such a condition of things is very often seen after influenza, but any fever may act in the same way and produce the same results.

An accident, again, such as a broken leg, especially if it comes near the time of life at which, in any case, nutrition would naturally begin to fail, will often serve to precipitate the same state of things.

And this condition of lowered combustion and deficient nutrition is just that in which any microbe that comes past, is able to take root and flourish, and the sufferer soon finds perhaps that phthisis or some other microbic malady is added on to his list of troubles.

This is probably the way in which some families of children get one disease after another, until they have run through nearly all the exanthemata, each fever leaving behind it a depression of nutrition, which predisposes them to take the next.

In a word, Bright's disease is a result of our meat eating and our tea drinking habits, and as these habits are common, so also is the disease, and much more common, I believe, than available statistics at all serve to demonstrate.

The relationship of Bright's disease to exercise is not very intimate; but exercise when it produces fatigue produces also collæmia and migraine, and migraine, especially if accompanied by albuminuria, is but the first stage of Bright's disease.

But the effect of exercise is dependent on diet, *i.e.*, on there being some uric acid available for solution in the blood. On a vegetarian diet or one in which milk is the only animal food, exercise cannot produce severe collæmia, and then it will produce relatively little fatigue and no headache or albuminuria; so that it is only when indulged in by those who live on a diet containing much meat and tea that exercise and fatigue can do harm (see chapter viii.).

I believe that the albuminuria which exercise produces, is brought about in exactly the same way as the fall of urea and the fatigue which it also produces.

The fall of urea is proof of defective metabolism and combustion, and carry this a little further we shall get not only deficient formation of urea, but the albumen of the blood will be imperfectly metabolised and will begin to diffuse and be passed in the urine;

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and carry it one step further still, and the blood elements themselves will begin to disintegrate, and we get paroxysmal hæmoglobinuria or its equivalent; and of this the causation is in all cases the same, namely, defective combustion from defective circulation, which again is due to excess of uric acid in the blood, which explains the excess of uric acid found in the urine in these cases.

Speaking of migraine reminds me that fatigue has often been observed to precipitate in exactly the same way the fits of epilepsy.

Clothing affects Bright's disease merely to a slight extent, according as it acts with collæmia in causing a deficient circulation in the skin, and thereby promotes a deficient metabolism in this important tissue, or according as it acts against the uric acid, and tends, as for instance, the warmth and equable temperature of bed does, to keep the skin well supplied with blood, in spite of a certain amount of vascular obstruction by uric acid.

Clothing which is too warm promotes collæmia by increasing the alkalinity of the blood; on the other hand clothing which is too light will cause retention of uric acid which will be followed at some future time by uricacidæmia and collæmia. But when there is not much uric acid in the body to be affected by clothing its chief effect is to keep up the temperature of the skin and to some extent to antagonise the evil effects of uricacidæmia.

Climate acts in very much the same way, for cold and damp chill the skin and also cause increased precipitation of colloid uric acid, thus in two ways tending to diminish its nutrition and metabolism. Therefore a cold climate aids uric acid in producing defective function and nutrition and eventual atrophy of the skin, while a warm one, on the other hand, tends to prevent these effects; hence Dr. Solly (prev. ref., p. 170) is right in recommending a warm dry climate.

Then, again, a climate in which there are great and sudden fluctuations of temperature is one in which there will be corresponding fluctuations in the excretion of uric acid and in the amount passing through the blood.

A steady elimination keeping pace with formation and introduction is better; but best of all is the same steady elimination with little or no introduction, so that the body and blood get clear, and remain so continually.

With regard to atrophy of the skin so much stress has been laid upon its thinness and wasting in Bright's disease by the late Professor Semmola and others, that it occurred to me that it might be possible to measure the thickness of the skin in the living, and I

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accordingly went to Mr. Hawksley, and he made an instrument for me which he calls a "dermimeter," by adapting one used by scientific instrument makers for measuring the thickness of microscopic glasses; and with this I have made a few observations which, so far as they go, show a relatively thin skin in Bright's disease. Thus May P., aged 11 years, in the last stage of Bright's disease (large pale kidney), had a skin measuring $\frac{8}{100}$ millimeter; while Martha V., of the same age, surgical patient, with periostitis and much wasted, had a skin of $\frac{11}{100}$ millimeter, both measured on the back of the hands.

It is obvious that this pathology, which makes Bright's disease a defective combustion throughout the tissues of the body, while this combustion is largely influenced by uric acid, and is therefore to a large extent within our control, makes the prognosis in this disease not only more definite and distinct, but also more hopeful.

When Bright's disease is acute, and when we see it before hopeless structural changes have taken place in the heart and great metabolic tissues there is only one way in which we may fail to cure, and that is by failing to clear the blood of uric acid; but with the knowledge we have, and still more with the knowledge we may soon hope to acquire, this failure should be quite rare, and therefore the prognosis of the acute disease when seen early is fairly good.

In the chronic disease or in advanced stages of the acute, cure is impossible; but we can almost certainly prevent the mischief from going any further, and by diminishing the metabolic needs of the body can hope to prolong life with a fair amount of comfort and happiness to something near its natural term.

As regards treatment, there is only one indication, viz., to clear the blood of uric acid and keep it clear, and beside this one all other indications sink into absolute insignificance.

No doubt it is of some importance to keep the surface warm by means of climate and clothing, and so neutralise to some extent the evil effects of obstructed capillaries on the nutrition and function of the skin, and heat also directly diminishes collæmia; but uric acid controls the circulation in all the tissues of the body, and not in one only, and we must never sacrifice the greater to the less, as was done in the case of Ada P., where the hot air baths given for the good of the skin were allowed to keep the blood flooded with uric acid (see fig. 63) to the detriment of all the other tissues and their metabolism.

The drug on which I chiefly rely to clear the blood of uric acid is

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mercury, and it will have been seen that I have used it for this purpose both in physiology and pathology.

The iodide of mercury also seems to be more powerful than other salts as we have the combined retentive action of iodine and mercury (see figs. 17 and 21).

Given freely and where it is well taken and does not cause mercurialism or gastro-intestinal disturbance, it will not very often be found to fail in clearing the blood of uric acid and freeing the capillaries.

When it quickly causes mercurialism, or when it causes gastro-intestinal irritation and diarrhœa or increases any that was previously present, it quite fails either to clear the blood of uric acid or to do the least good for the Bright's disease.

I had an instructive case with reference to these points under my care a few years ago, of a man who had been in India and suffered from dysentery and who came under my care suffering both from chronic dysentery and from chronic Bright's disease (large pale kidney).

I should have no doubt that his Bright's disease (*i.e.*, defective combustion) was the result of the intestinal irritation with the chronic collæmia which it helped to keep up.

I treated the dysentery with astringent injections, and having got it within moderate limits I proceeded to try and treat the Bright's disease, and among other things I used the hst. hydrarg. perchlor. c. pot. iod.

This for about a week appeared to do good, it lowered his blood pressure, freed his capillaries, and increased his combustion; but at the end of that time the dysenteric trouble increased, and then the drug soon lost all power over uric acid, the capillaries and the combustion.

When mercury or its iodide fail from these causes, other metals may be tried, but, as I have pointed out, they all, like mercury cause or are apt to cause intestinal irritation and to fail in the same way.

The best thing to do in this case is to treat the gastro-intestinal troubles directly, and when they have been got into a quiet state to give salicylates and acids, as in the case of Charlotte W., or gastro-intestinal trouble should be treated with salicylates and bismuth, and acids given later on.

There is also probably no objection to a little opium for the intestinal troubles so long as it is given with the salicylates, which will prevent its dangerous rebound (see chapters ii. and iii. and fig. 34).

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I am indebted to my colleague, Mr. D. H. Goodsall, for the observation that mercury does not salivate or cause the other troubles of mercurialism so long as iron is given with it, and he gives them together as the perchlorides, or the sulphate of iron with sulphate of magnesia concurrently.

I have not myself had any experience of this treatment, but as regards uric acid the two metals act in the same way, and mercury is such a powerful remedy in Bright's disease that anything that will enable us to continue its administration may be most valuable. I see also that a similar combination of the perchlorides of these two metals is recommended in the work of the late Dr. Fothergill as being useful in syphilis.

The main point in the old pathology treatment of Bright's disease was the administration of diuretics which were supposed to flush out the kidney and relieve its irritation, and this was very good treatment, not because the drugs really did good in the way supposed; but because, as I have shown, every drug which causes a diuresis does so by clearing the blood of uric acid and freeing the capillaries, so that the drugs given did not merely free the circulation through the kidney and cause diuresis, but they at the same time freed the capillaries all over the body and thus promoted increased metabolism and combustion in all the great metabolic tissues.

The action of iodide of mercury in diminishing the excretion of uric acid and causing diuresis, and at the same time promoting increased metabolism and combustion is very well seen in fig. 49.

If we succeed in clearing the blood of uric acid and thus promoting a free metabolism and combustion and keeping them going, we have cured Bright's disease: if we fail to clear the blood of uric acid we fail to cure, and the same may be said of anæmia and the diseases treated of in the previous chapter, as well as of the conditions considered in chapter viii.; from which also we see that it matters little how we clear the blood of uric acid, so long as we do clear it.

But if combustion has been so long defective that atrophy of tissues has taken place it is impossible to cure.

Dropsy hardly needs any special treatment, it is but a result of obstructed capillaries and heart failure (relative or absolute), and if we can free them and strengthen the heart it will disappear; if the heart is strong and its action slow, clearing the blood of uric acid will suffice to remove the dropsy, which is not often very marked under these conditions, but where the heart is weak and failing and acting quickly, it may be necessary to help and strengthen it with

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strychnia either internally or subcutaneously, at the same time that we free the capillaries.

When ascites is present to any marked extent it will act as a mechanical hindrance to the circulation and will have to be removed by tapping before drugs can be expected to have much effect, but ascites generally comes late in the disease, and is a sign of very defective circulation and relatively weak heart; there is therefore all the more reason to treat it promptly.

Diet has in this disease a double importance, for it is not only the means by which we can regulate the introduction and formation of uric acid, and so the quantity available for mischief by getting into the blood; but by limiting animal food to milk only we appear to be able to supply all the albumens required, in a form which, according to Semmola, demands the smallest amount of metabolic activity to render it a suitable constituent of the blood and tissues.

In acute cases milk should for a time be the only animal food and the only food at all; but when the albumen has been reduced to a mere trace, bread stuffs, cereal foods and farinaceous prepared foods, with cheese and pulses, and fruit may be added; and this diet may have to be continued during the rest of life.

In chronic cases where there are headaches, either migrainous or uræmic, these may be taken as the guide to treatment, and such diet made use of as serves to reduce them to the lowest point both as to frequency and severity, and the treatment is in these cases exactly the same for morbus Brightii as for migraine; in neither condition will it ever again be possible to take animal tissues to the extent that is usually done in ordinary diet.

These alterations of diet will also fulfil another indication as they will increase the alkalinity of the blood and promote the gradual solution and elimination of the uric acid previously retained and stored in the body, and this elimination will be so gradual that as a rule it will do no harm.

In some cases when the mercury or other drug which clears the blood of uric acid is left off we shall get a rebound and find the blood flooded with uric acid and a relapse of the disease imminent; and it may occasionally be necessary to give salicylates either with or in sequence to the retentive drugs to prevent this.

But in most cases, I think that if the blood has been kept clear of uric acid for a considerable time, say two months, the fires will meanwhile have burnt up brightly, and combustion will be so good that the uric acid will only be able to pass slowly through the blood,

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and will not, therefore, diminish combustion and damp down the fires to any very serious extent.

It is necessary however to bear these facts and possibilities in mind, so as not to be taken by surprise if a relapse should in this way occur; in this case we should repeat the retentive drugs and follow or combine them with a short course of salicylates.

With regard to salicylates, I may just mention that I have never seen them do any harm; when they increase the uric acid they diminish for a day or two the urinary water, and then the albumen may appear to be increased, but I have never found that it was absolutely increased in relation to urea.

If they ever do any harm, it is when given with alkalies, or in conditions of much debility and depression where the alkalinity of the blood is high; then some of the urate they sweep out of the tissues may combine with the alkali in the blood, and this will obstruct the capillaries and diminish combustion.

My rule is to give salicylates in conditions of low alkalinity of the blood, or to give them with ammonia which raises the acidity of the urine, or in alternate doses with acids or salts of the mineral acids, or as above mentioned along with a little opium.

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CHAPTER XIV.

Glycosuria and Diabetes Mellitus.

Glycosuria and diabetes mellitus have interested me for a considerable time, because they appear to have some relation to uric acid, a relation which, as in the case of headache and mental depression, has been noted by several observers.

While thinking over this relation I was led to try the effects of salicylate of soda (without any knowledge that it had been previously used by others), and the results in many cases (see paper on "The Use of Salicylate of Soda in Diabetes Mellitus and its Connection with Gout," *St. Barthol.'s Hospital Reports*, vol. xxv.) were so remarkable that this seemed to me to form another link in the chain connecting this disease or disorder of function with uric acid.

Sir A. Garrod says ("Gout and Rheumatic Gout," p. 472): "In the course of practice I have seen several cases in which gouty patients have become affected with saccharine diabetes, or glycosuria," and he narrates the case of a gentleman of 60 who had had gout for twelve years when diabetes suddenly came on, and for more than four years there were no gout attacks. Then the diabetes was checked and the gout soon returned.

Sir W. Roberts says ("Urinary and Renal Diseases," ed. iv., p. 256): "The subjects of obesity and of the gouty diathesis are very prone to a mild form of diabetes."

Professor Latham (*British Medical Journal*, 1886, vol. i., p. 737) has written about a form of diabetes which originates, he believes, in some error in the metabolism of muscular tissue, and he says that in this form of the disease salicylic acid treatment is of the greatest importance, and remarks that these patients often have excess of uric acid in their urine, and suffer from neuralgic pains in the joints and limbs.

Then the late Dr. James Anderson in an extremely interesting paper in the *Ophthalmic Review* (February-April, 1889), mentions in many places the connection of gout with diabetes, and at p. 18

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says: "Many clinical facts go to show that gouty arthritis and diabetes mellitus are in certain cases merely transformed symptoms of the same diathesis, not present at the same time but one taking the place of the other." This, as will be seen, corresponds exactly with my previous quotation from Sir A. Garrod.

Dr. Anderson also makes several interesting quotations from Fagge's "Principles and Practice of Medicine," to the effect that both gout and diabetes are due to disorder of hepatic function.

Now it seems to me that some hyperæmia or congestion of the liver is nearly the only fact in the morbid anatomy of diabetes, about which there is any considerable unanimity of opinion among pathologists. Thus, as mentioned by Sir W. Roberts (previous reference, p. 275-276), Sir S. Wilks believes that the liver of diabetes can be distinguished by its appearance (especially its firmness and dark colour) from that of other diseases. Dr. Dickinson sees signs of long-continued hyperæmia in the livers of diabetic patients, and Prout observed a gorged condition of veins terminating in the portal system in the same class of patients.

Dr. Saundby, in his lecture on the "Morbid Anatomy of Diabetes," says that the liver is generally enlarged, though he lays special stress on the wasting of the pancreas, and urges its further examination (*Lancet*, 1890, vol. ii., p. 381).

Dr. Pavy again (*British Medical Journal*, 1883, vol. i., pp. 863-866) credits diabetes to a vaso-motor paralysis of the chylopoietic circulation which allows arterial blood to be supplied to the liver in place of venous.

It seems probable also that the various brain and peripheral lesions which sometimes cause glycosuria act by affecting directly or indirectly the liver circulation, as Frerichs (*Uber den Diabetes*) points out that puncture of the fourth ventricle only causes glycosuria when the liver contains glycogen.

Now there is evidence to show that some amount of congestion of the liver is very commonly associated with gout, and speaking of the symptoms of the most common form of gouty dyspepsia, Sir A. Garrod says (*loc. cit.*, pp. 231-232): "These are generally accompanied with sluggish circulation in the portal system and congested livers;" and he further speaks of fulness and tenderness in the hepatic region as symptoms of this congestion.

The occasional association of glycosuria with ague is, perhaps, an instance of some influence on the circulation of the liver and spleen causing glycosuria.

We seem, then, to have arrived at this point, that there is a

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condition of liver congestion which is common in gouty dyspepsia, and bears, no doubt, some relation to uric acid and its presence or absence from the blood.

On the other hand, we have glycosuria in the pathogeny of which congestion of the liver is a very common feature, and this glycosuria has been noticed by several observers to bear a relation to "the uric acid diathesis" and to gout.

Now the relation of glycosuria to gout is, as we have seen, that the one alternates with and replaces the other; where there is glycosuria there is no gout and *vice versâ*. Now gout corresponds with the precipitation of urate in the joints and its comparative absence from the blood, so that with absence of urate from the blood there is no glycosuria.

But when a gouty patient goes for some time without an attack in his joints, he does so probably because something has increased the alkalinity of his blood, so that it now takes up instead of depositing urate, and there is collæmia and excessive excretion of urate in the urine; this is the opposite condition to that of gout, and with this there may be (as we have seen) glycosuria.

So that glycosuria corresponds with excess of uric acid in the blood (uricacidæmia and collæmia), the opposite condition to that of gout.

But congestion of the liver also corresponds to excess of uric acid in the blood; for Sir A. Garrod says (*loc. cit.*, pp. 231-232): "The more prominent symptoms of the dypepsia connected with the uric acid diathesis may be thus summed up: heartburn and eructations, oppression, and frequently sleepiness after food; a feeling of distension in the epigastrium at times accompanied with tenderness; some fulness over the hepatic region, the edge of the liver projecting a little below the ribs, and being occasionally tender to the touch; the tongue much furred, red at the tip and edges, a disagreeable and clammy taste in the mouth, and the saliva and buccal secretion often more adhesive than natural." In two words, there is dypepsia with its natural result, uricacidæmia and collæmia; this latter accounting for the oppression and sleepiness and the scanty saliva and clammy taste in the mouth; and in chapter xiii. (p. 439) I have given notes of a case in which marked enlargement of the liver accompanied a uric acid storm, and pointed out that I had myself had very similar experience of the effects of collæmia on the liver.

Now Dr. W. M. Ord has pointed out (*British Medical Journal*, 1889, vol. ii., p. 965) that general high tension may cause an excess of blood in the liver and so glycosuria; and I have shown that

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arterial tension is directly as the uric acid that is circulating in the blood, therefore collæmia will cause high tension, and this will produce congestion of the liver and glycosuria (p. 440).

The causation of glycosuria is thus theoretically complete, and it agrees with the experience of clinical observers that it alternates with gout and corresponds with the absence of gouty arthritis, that is, with the presence of collæmia.

I may say also that my experience agrees absolutely with that of Sir A. Garrod, and that in my own case congestion of the liver always corresponds with collæmia, and to such an extent is this the case that I have come to believe that I can produce some congestion of the liver at pleasure by affecting the uric acid.

If collæmia by hampering the heart and causing back pressure on the venous system does in this way produce congestion of the liver and of the whole chylopoietic circulation, it is easy to see that it may have a causal relation to troubles beyond the liver, such as piles and pruritus ani; and I was much interested to hear from Mr. Maitland Thompson, of Hemel Hempstead, that he had had considerable experience and was prepared to answer for the intimate connection of pruritus ani with meat eating. In several cases reduction of meat had in his experience produced great and permanent relief, but in one case where the patient refused to alter his diet all kinds of treatment, including various surgical measures, had given no relief, and I have myself had similar experiences.

Similarly there seems to be reason to believe that the enlargement of the prostate which gives so much trouble in men past middle life is often associated with (? caused by) high blood pressure and collæmia, and is often very greatly relieved by a milk or a uric acid free diet which lowers the blood pressure; and Dr. J. Haddon, of Hawick, N.B., has kindly told me that this is most certainly his experience of such troubles.

It is interesting to remember in this connection that cirrhosis of the liver is sometimes attributed to sclerosis of arterial capillaries (*Gazette des Hopiteaux*, Aug. 4, 1888), and that the late Professor Semmola was for a long time in the habit of treating this trouble with milk diet and large doses of iodide of potassium, which would free the capillaries (see *Progrès Médical*, Dec. 1888, p. 533).

But in Dr. Ord's paper above referred to, there are many points of very great interest, some of which I must mention at greater length, as I believe that the knowledge which we have now obtained of the action of uric acid on the capillaries will enable us to explain a great many of them.

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It had occurred to me some time ago to enquire if glycosuria has this causation (*i.e.*, is due to congestion of the liver, which again is due to the general high blood pressure produced by uric acid), ought we not to meet with it in that disease in which high blood pressure is more marked than in any other, namely, chronic interstitial nephritis? From my own experience I was not able to answer the question, but on turning to Dr. Ord's paper, I was interested to find that he says (previous reference, p. 966): "We not infrequently find that people presenting in a typical form the symptoms of contracting granular kidney have also glycosuria." I have certainly seen several cases in which albuminuria and glycosuria appeared to alternate with each other, but whether these were cases of granular kidney I could not say; they appeared to me, however, to be almost certainly gouty cases with high blood pressure.

Then Dr. Ord narrates, at considerable length, a case in which typical angina pectoris co-existed with glycosuria, and it would be impossible to find a case more to the point as regards the argument I am here bringing forward.

The patient, age 62, suffered at first along with his glycosuria, from low spirits and sleeplessness (very marked signs of collæmia). Then he had an attack of quinsy, in which, as is usual during fever, the sugar disappeared, but was replaced by albumen (note the collæmia would also disappear in the fever).

A little later he began to have angina, which afterwards during an attack of gastric catarrh became very severe.

Now there is hardly any condition which is more certain to produce intense collæmia than gastric catarrh (see pp. 136 and 332), and this would completely account for the increase of the angina, and with this increase of angina there was an increase of the amount of sugar in the urine.

I should be inclined to explain the sequence of events in this most interesting case as follows:—

First, slight collæmia as evidenced by irritability, depression and loss of sleep; this producing general high blood pressure which, through its effects on a weak heart, produced back pressure and congestion of all behind it, hence congestion of the liver and glycosuria.

Later on the congestion of liver produced secondary congestion of the stomach and duodenum, and this, acting with some other slight cause, brought about gastric catarrh.

This last, again, produced nausea and vomiting which resulted in a great fall of urea and acidity; and again, as the result of the

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fall of acidity, the collæmia became intense; this more and more overtaxed and dilated the heart, the angina increased and became incessant, there was consequently increased congestion of the liver and increased glycosuria, and the patient finally died in an attack of angina.

Dr. Ord is inclined to invoke the nervous system as the cause of the high tension, though he says: "But in a preponderance of the cases presenting glycosuria together with symptoms of angina, the evidence of primary neurotic disturbance has not been so strong."

I have shown that uric acid will obstruct the capillaries and produce high blood pressure, and we had here in action all the causes which will produce collæmia, and all the signs of its presence, and I have no doubt that the urine also contained a great excess of uric acid, so that it appears to me to be quite unnecessary in any such case to invoke the unknown action of the nervous system. I do not deny that the nervous system can produce a somewhat similar effect, but I assert that in the case in point, uric acid, and uric acid alone, did produce all the symptoms from the irritability, mental depression and loss of sleep to the congestion of the liver and glycosuria and the dilatation of the heart and fatal angina.

In an interesting paper on "Angina" ("International Clinics," second series, vol. vi.), Professor T. J. Mays points out that the effects of uric acid on the circulation afford a very complete explanation of several important points in its causation, as it is accompanied by a slow pulse, and is very often worse in the morning hours when there is most uric acid in the blood, and, further, like migraine and epilepsy, it may be preceded by feelings of exaltation and well-being (see chapters vi. and vii., and the causation of fatigue and chloroform syncope, chapter viii.).

Two interesting cases in which angina occurred along with gout and diabetes in two fat individuals are recorded by Ebstein in *Berlin Klin. Woch.*, June, 1895, and mentioned in the epitome of the *British Medical Journal*, 1895, vol. ii., p. 17, it seems to me that in these cases the angina was the result of high blood pressure produced by collæmia, and the diabetes and the fat were the results of the defective combustion it produced.

With regard to high blood pressure, almost every case of diabetes I have seen has presented its signs to a more or less marked extent, and whether the heart acts quick or slow there is always a very loud second sound at the aortic base.

In some cases, just as in Bright's disease, there is bradycardia as a sign of the high pressure, but in more cases there is some heart

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failure with quickened action, though the aortic second sound remains very loud and the artery is full between the beats.

But allowing for the debilitating effects of the disease, and the consequent heart failure, I believe that the signs of high blood pressure, either actual or virtual, are quite as marked in diabetes as in Morbus Brightii, and in fact I think that almost the highest blood pressure I have ever seen is that of a young man at present under my care with diabetes whose radial artery measures 2·2 mm., and his pulse is often below 60; he has not as yet been much debilitated by his disease, as it has apparently not existed for more than three or four months.

His high blood-pressure led me to put him on the iodide of mercury, which, as we have seen in the previous chapter, is so useful in the high pressure of Bright's disease, and up to the present he has done so well on it, that I shall certainly give this drug a further trial in other cases of diabetes.

An interesting case is also recorded in the *Lancet* of September 28, 1895, in which thyroid extract administered for myxœdema seemed to make anginal attacks more severe, and what I have said with reference to fig. 29 sufficiently explains this result (see also my letter to the *Lancet* on this point, October 5, 1895).

I have now shown that glycosuria has been observed to alternate with gout, and that this alternation probably means that it is contemporaneous with excess of uric acid in the blood (collæmia).

My thesis also rests on the further facts of which I shall now give details—(1) that acids (which, as I can show, clear the blood of uric acid and prevent collæmia) are useful in glycosuria, and that certain mineral waters containing excess of sulphates which, like acids, also clear the blood of uric acid are equally useful in the cure of the disorder; and (2) that salicylates, as observed by myself and others, are very useful both in glycosuria and diabetes, and that they also clear the blood, liver, and other organs of uric acid.

The point about which there seems to be the least room for doubt is that glycosuria alternates with gout, and is commonly contemporaneous with collæmia; and supposing that the collæmia is the cause of the glycosuria there are obviously other ways in which it may bring about this result besides that sketched out above in which it produces congestion of the liver. In this case there is excess of sugar in the blood and glycosuria because excess of sugar passes from the liver; but supposing that the liver is not thus affected, and that only the normal amount of sugar passes into

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the blood, it may still come to be in excess in the blood if it is not used up and destroyed in the general circulation; and it seems to me that uric acid, by producing obstruction of the capillaries, may, and probably does, interfere to an important extent with the metabolism of the muscles, skin, etc., and may thus bring about glycæmia and glycosuria through deficient destruction of sugar. At this point I think there is an interesting parallel in the pathology of "curare diabetes" in which the excess of sugar in the blood is supposed to be due to its not being used up in the paralysed muscles (see *Archiv. fur Anat. and Physiol.*, 1891, p. 476).

Before leaving these theories I will mention one fact that seems to me of interest, namely, that as observed by Sir W. Roberts ("Urinary and Renal Diseases," p. 255), women suffer less than men after the age of 45; he attributes this relative immunity to the early decline of sexual activity; but I have shown that menstruation and especially dysmenorrhœa produce collæmia (see figs. 30 and 31), and a cessation of these disturbances may mean that the blood remains at this period in women moderately free from uric acid for some time, and besides, owing to the previous excretion of some excess of uric acid every month, women, about and for some time after the menopause, will not have so much uric acid in their bodies available for excretion as men of the same age; but I shall have to speak of the effects of menstruation again. (See case Mrs. C., further on). With regard to the effects of acids, it is recorded, as I have mentioned before (*Practitioner*, 1891, vol. i., p. 193), that Sir W. Foster, in 1871, gave several patients suffering from diabetes considerable doses of lactic acid, which improved the diabetes, but produced considerable pain and swelling in the joints; and this most valuable record proves several points of importance: first, that diabetes or glycosuria was present in these cases with excess of uric acid in the blood, or the acid would have had nothing to act upon; secondly, the acid acting, as I have shown that it does, in diminishing the alkalinity of the blood and reducing its power of holding uric acid in solution, caused it to be deposited or retained in the joints where its presence gave rise to an arthritis indistinguishable from that of acute rheumatism (see chapter xvi.).

We have here, I think, a strong light thrown upon the causative connections of both rheumatism and diabetes: the condition (rising acidity) which cleared the blood of uric acid produced the one disease while relieving the other; just as mental depression, which is due to collæmia, clears up when an attack of gout is produced.

I have also used acids with apparent benefit in some cases of

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glycosuria under my own care, and I was led to do so by reasoning that they would probably clear the blood of uric acid and have to some extent the same effect as salicylates, and without having any knowledge of Sir W. Foster's cases.

In my paper in *St. Bartholomew's Hospital Reports* (vol. xxv., p. 11, *et seq.*) I have pointed out what has been said about the great effects of certain waters as those of Contrexéville, Carlsbad, and Brides-les-Bains in curing diabetes, and have suggested that these waters owe their efficacy to the excess of sulphates they contain; as sulphates, especially sulphate of soda, act as I have shown, the part of acids, interfere with the solubility of uric acid, and clear the blood of it (see *Medico-Chirurgical Trans.*,vol. lxxi.). In the same way these sulphate waters may cure or relieve chronic arthritis by keeping the blood clear of uric acid so that none can be brought to the joints in the blood stream to increase the irritation in them; but if a patient has much uric acid in his blood when he begins to take these waters they may produce an attack of gout, thus clearly showing the way in which they relieve diabetes, by acting like the lactic acid above mentioned. In exactly the same way a meat diet relieves some cases of arthritis (gout or rheumatism) by acting as a stimulant and keeping the blood clear of uric acid for a time, and it seems probable that a diet like that of diabetes, which consists so largely of flesh, will have a similar stimulant action and relieve by keeping the blood clear of uric acid for a time, as well as by merely replacing the starches and sugars.

Before I go into the action of salicylates and give notes of my cases treated by them, I may perhaps mention shortly a few points about their effects on uric acid.

A salicylate, then, increases the solubility of uric acid, and must for a time increase the quantity contained in the blood; but though it does this the effects of uric acid in the blood seem to be modified (possibly by its being present as salicyluric acid and in a state of complete solution) and it neither affects the capillaries so greatly as uric acid combined with an alkali only, nor does it produce any headache.

But though we get salicyluric-acidæmia (see remarks on the chemistry of salicyluric acid, p. 36) as the first effect of giving a salicylate this does not last very long; the uric acid is in a condition of perfect solution, it passes quickly through the kidney and out of the body, and, as I have pointed out, the great excretion of urate under salicylates occurs on the first two or three days of their action, and after that excretion falls away almost to the level of formation;

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thus it comes about that after the first day or two of their action there is never any great amount of urate in the blood.

The effects of salicylates, therefore, resemble those of acids and sulphates in that they clear the blood of uric acid, and they all have this also in common—that they diminish or stop glycosuria or diabetes.

There are one or two other points of interest with regard to these substances which I may just mention. Acids are commonly used in conditions of slight congestion of the liver; sulphate of soda is supposed to have a special action on the liver, and salicylate of soda again is said to render the bile more fluid and watery; but all of them, acids, sulphates, and salicylates, as we have seen (chapters ii. and iii.), increase the urinary water, and I have suggested that they produce this effect by freeing the capillaries of the kidney from the obstruction produced by uric acid; is it not probable, I might say certain, that they produce precisely the same effect on the capillaries of the liver, and for that matter on those of the whole body? Hence, acids and sulphates relieve congestion of the liver by improving the circulation through it, and salicylates render the bile more fluid by the same action, just as they make the urine more copious.

But the salicylates have this great advantage, that they clear the blood of uric acid by removing it from the body while the acids and sulphates clear the blood (as do also opium, mercury, the iodides, iron, lead, and lithia, &c.), by retaining it in the liver, spleen, joints, and other tissues.

Prominent among other drugs that have been found useful in diabetes are opium and antipyrin, and I have shown (pp. 54 and 61) that they raise the acidity of the urine, and probably as regards uric acid act the part of acids and clear it out of the blood; therefore all drugs that are useful in diabetes have this effect in common, that they clear the blood of uric acid, and clinical experience and observation go to prove that glycosuria is associated with an excess of uric acid in the blood, and may in some of the ways I have suggested be actually due to such excess; its well-known relationship to gout and the uric acid diathesis being thus susceptible of a simple explanation. And there are two pathological conditions, which having the same action as the drugs just mentioned, in clearing the blood of uric acid, also for a time put an end to glycosuria or diabetes. One of these conditions is a fever, and the other is the effect produced on metabolism by a surgical operation. The fact that these conditions do diminish the sugar in diabetes was

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mentioned at a meeting of the Royal Medical and Chirurgical Society, in October, 1892 (see *Lancet*, and *British Medical Journal*, October 29), but no explanation was attempted.

After what I have already said as to the action of fevers in diminishing the excretion of uric acid in the urine, and clearing it out of the blood, and consequently freeing the capillaries, causing diuresis and a soft pulse, and a general increase of metabolism, both in the liver and other tissues, and of the post febrile rebound which follows their departure with excessive excretion of uric acid, slow high tension pulse, scanty urine and subnormal temperature, and diminished metabolism, in all of which points their effects exactly resemble those of opium, mercury, the iodides, and other drugs; I need not do more than point out that, like these drugs, fevers supervening upon a glycosuria or diabetes, diminish or stop the excretion of sugar, and the fact is as well known as the explanation is simple.

There is one point, however, that I would specially like to bring to the notice of those who may make clinical observations on the effects of fevers on the excretion of uric acid, namely, that the blood and urine are most completely cleared of uric acid during the first few days of the fever, and it is then that the pains resulting from their precipitation on joints and other fibrous structures are most likely to be met with. In my own person I have several times correctly diagnosed a slight rise of temperature from pricking and shooting pains in my joints with a diuresis.[1]

But there may be a considerable amount of uric acid, both in the urine and in the blood as the temperature comes down, even while it is still a degree or two above normal; for the solubility of uric acid in the blood depends on its alkalinity, and for any given alkalinity the quantity in solution will be greater, the more urate there is available for solution.

Now the rapid metabolism at the onset of a fever quickly diminishes the alkalinity of the blood, for I have shown that, as regards the urine, urea and acidity practically always rise and fall together, because they are two results of the same metabolism,

[1] Thus the first rise of temperature may run the urine up from, say, 50 cc. an hour to 150 cc. in the same time, and this continues for 3, 4, or 5 hours; but then the supply of water is exhausted, and for the next 24 to 36 hours the blood is very concentrated and the urine scanty. The extent and duration of the diuresis thus obviously depend on the quantity of fluid available, and it is only when there is dropsy, as in the case narrated on p. 446, that it can last very long.

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hence there is at the beginning of a fever considerable storage of uric acid in the body.

But, as time goes on, and the patient becomes worn out with the fever and deficient income of food, metabolism will run down in spite of the temperature being still raised; the alkalinity of the blood will again increase, and it will take up much uric acid, partly because of its altered reaction, and partly because the stores of uric acid in the body have been increased at the first onset of the fever, and so there is plenty of it to get into the blood, hence it often does get into it and puts an end to the dicrotism of the pulse, as noticed by Marey, Mahomed and others, some little time before the temperature touches normal. But if these facts are not kept in mind, if the uric acid is estimated with sole regard to the fever but no regard to the metabolism, the diminished excretion at the beginning of the fever may be partly balanced by plus excretion near its end, and most contradictory results will no doubt be obtained. My results show for instance, that early in pneumonia there is almost no uric acid in the blood, and yet after death there is more in it than after almost any other disease. We can now see that the fluctuation in one direction is the result of the previous fluctuation in the other.

A fever therefore diminishes the sugar in the urine of diabetes, because by clearing the blood of uric acid and freeing the capillaries, it quickens the metabolism throughout the body, and up goes urea as a result of this, just as we have seen that it goes up when the blood is cleared of uric acid by any other means, hence the glycosuria diminishes or disappears, especially during the rising temperature of the onset of the fever, because the combustion of sugar is complete. Similarly when excess of uric acid in the blood diminishes the metabolism throughout the body, urea, as we have seen, goes down (figs. 39 to 42).

Now the effect of a surgical operation on the metabolism is practically the same as that of a fever. I was much struck with this some years ago, when I chanced to obtain for another investigation the urine of a woman, for one or two days before and after the operation of abdominal section. The rise of urea after the operation was enormous, reaching twice or even three times its previous height, and I explained this to myself by supposing that there was very active metabolism at the seat of operation, and that the patient was thus placed on a highly nitrogenous diet at the expense of her own tissues.

I have unfortunately mislaid the notes of this case, and cannot now give the exact figures; but Dr. Young, formerly resident

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medical officer of the Royal Hospital for Children and Women, kindly investigated some cases for me, and I am indebted to him for the following notes:—

E. K., age 47	...	June 6	...	264 grs. urea.
,,	...	,, 7	...	124 ,,
(Plastic operation for ventral hernia.)				
,,	...	June 8	...	422 ,,
,,	...	,, 9	...	528 ,,
,,	...	,, 10	...	401 ,,
,,	...	,, 11	...	322 ,,

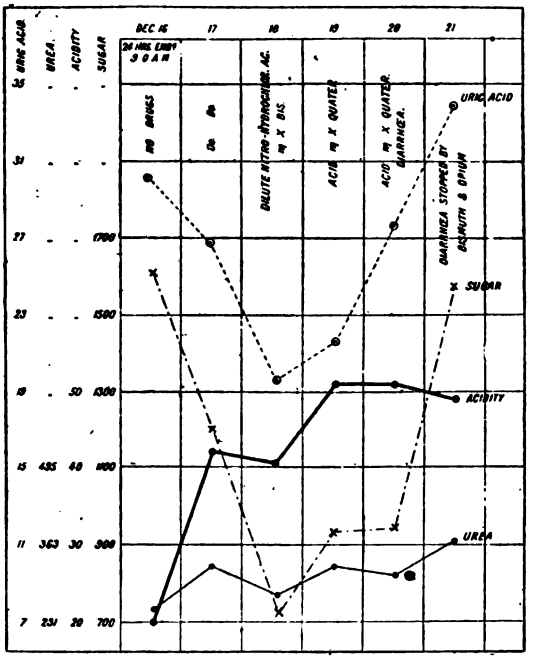

FIG. 53.—CURVES OF EXCRETION OF URIC ACID AND SUGAR IN A CASE OF GLYCOSURIA.

Sarah H., age 49. Ovarian Tumour.

Before operation	...	...	...	151 grs. urea.
1st day after ,,	...	...	...	192 ,,
2nd ,, ,, ,,	...	..	...	354 ,,
3rd ,, ,, ,,	...	...	...	188 ,,

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M. H., age 56. Ilio-femoral abscess.

Before operation	...	...	...	232 grs. urea.
1st day after ,,	...	...	...	276 ,,
2nd ,, ,, ,,	...	...	...	452 ,,
3rd ,, ,, ,,	...	...	...	345 ,,

In each of these cases the urea doubled after the operation, the greatest excretion of urea taking place on the second day after it; and for some cases in which the effects of an operation were still more marked, see *Lancet*, 1893, vol. i., p. 1,413.

Then, as I have shown, the acidity of the urine rises with the urea, and urates in the blood and urine vary inversely as the acidity, hence a surgical operation, which causes a marked rise in urea, will clear the urates out of the blood, free the capillaries and increase the metabolism.

I will now also give a figure to show the remarkable way in which, in a case of glycosuria, the uric acid and sugar fluctuate together.

The curves are from the case of Rebecca M., age 45, who was under my care at the Metropolitan Hospital in 1889, suffering from enlargement of the spleen, excess of white cells in the blood, and glycosuria.

I have also pointed out (p. 69) that in cases where the spleen is enlarged, there is nearly always a great excess of uric acid in the urine, and others have pointed out, just as I should expect, that it is in excess in the blood in these cases.

It follows, therefore, that this is just the condition of things in which we should expect to find just what we do find in this case—a glycosuria as the result of the uricacidæmia and collæmia, which is common in such cases.

On December 16 (fig. 53) we see that uric acid and sugar are both high, urea and acidity low; on the 17th urea rises a little and acidity still more, and with this there is a fall of uric acid and a fall of sugar. There must have been some cause depressing the acidity on the 16th, for it rises on the 17th out of proportion to the rise of urea.

Talking of low acidity reminds me of the fact of which we shall see instances among my cases, that patients suffering from diabetes or glycosuria, often say that alkalies, such as the bicarbonate of sodium or potassium, do them harm; and we see in this figure the way in which they do it, namely, by increasing the collæmia, and in this figure the uric acid is high, because the acidity is low,

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and the sugar is high because the uric acid is high. So that not only do all drugs, fevers, and surgical operations, which diminish collæmia, do good, but drugs like alkalies, which increase collæmia, do harm.

Some of my readers will probably remark that alkalies are often of great use in diabetes, and may reduce the sugar very markedly.

Now I have mentioned in previous chapters the effects of alkalies on metabolism in health, and the way in which they increase uric acid and diminish urea; is it to be doubted that they have the same effect in disease, and that when they reduce the sugar, as there is no doubt they may, they have done it by interfering with the digestion, absorption, and metabolism of food, and have reduced the urea quite as much, or even more than the sugar.

And in what I shall have to say presently on the use of salicylates in diabetes, I shall point out the great importance of estimating the urea as well as the sugar, and of not regarding as a curative effect a diminution of sugar which depends on an equivalent diminution of urea.

But to return to our figure on December 18th, the patient took ℥x. of acid. nitro. hydrochlor. dil. twice: urea fell a little and acidity also slightly, and would no doubt have fallen more but for the acid taken; uric acid and sugar fall decidedly and reach their lowest points.

On December 19th she took ℥x. of the dilute acid four times; urea rose a little, acidity more decidedly as the result of the acid taken; uric acid and sugar both rose a little, though uric acid bears much the same relation to urea that it did on the previous day.

On the 20th the patient again took ℥x. of the acid four times a day; but now she has some diarrhœa, so urea falls a little. Acidity did not rise; uric acid rose, but sugar remained about the same as on the 19th.

This is the only occasion on which uric acid and sugar did not move in the same direction, and I think this is due to there being, on account of the diarrhœa, a lessened absorption of food, and therefore a lessened income of sugar. (Compare previous remarks on the effect of alkalies.)

On the 21st the diarrhœa was stopped by means of bismuth and opium mixture, and urea rose; but acidity fell as the result of leaving off the acid and the effect of the diarrhœa on the previous day. Probably the acidity was really low in the early part of this day (21st), and this allowed of the large urate excretion which we see; later in the day, as the result of the opium, it rose sharply, and

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the balance of the two fluctuations resulted in only a slight fall of acidity in the whole twenty-four hours. I constantly meet with such results in my own experimental work on excretion. And lastly, on this day there is a great rise of sugar corresponding fairly well with the rise of uric acid.

Taking the whole figure, I think it must be acknowledged that the curves of uric acid and sugar run parallel to each other in a remarkable way, and some of my other cases to be given presently seem to show much the same thing.

I here therefore suggest that just as we saw in the previous chapter that albuminuria and Bright's disease may originate in a lowering of metabolism which brings about hetero-albuminæmia, albuminuria and nephritis, so also is glycosuria or diabetes due to a similar lowering of metabolism which hinders the final combustion of carbohydrates and, leaving them to circulate in the blood, produces glycæmia.

And as I have already pointed out in chap. xiii., p. 473, one and the same patient may have to-day albuminuria, and to-morrow glycosuria or *vice versâ*.

The lowered metabolism may in each case be due to uric acid, which brings about a deficient capillary circulation in all the great metabolic tissues: its evil effects being no doubt either increased or diminished by concomitant conditions.

We have already seen in previous chapters that the quantity of uric acid in the blood controls the formation and excretion of urea and the presence or absence of fatigue under exertion, and probably also the formation as well as the distribution of animal heat; it controls, in a word, the metabolism, nutrition, and function of the whole body, and thus accounts in the most simple manner for a whole series of physiological and pathological sequences.

In this connection there is a most interesting note in the epitome of the *British Medical Journal*, 1895, vol. i., p. 1, on Alimentary Glycosuria in Lead Colic. This has reference to an article by Brunelle (*Arch. Gén. de Méd.*, December, 1894) in which it is pointed out that the liver is implicated in lead colic because there are modified pigments in the urine, a subicteric tint in the conjunctiva and a diminished excretion of urea. Accordingly the author gave from 150 to 300 grs. a day of syrup, with the result of producing glycosuria in eleven out of twenty-one cases of lead colic. The glycosuria fluctuated with the colic and generally disappeared with it.

It would be difficult indeed to find an observation more interesting and instructive than that above quoted.

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The fall of urea would alone be sufficient to prove that there was severe collæmia present, even if we did not already know that in lead colic there is always a slow high tension pulse and all the other signs of collæmia (see fig. 13 and remarks on lead colic), and if we did not also know that collæmia is the one certain result of all colic and gastro-intestinal upset.

And the rest of this observation shows that these patients were, during the continuance of the colic, unable to burn up and metabolise the whole of this sugar, so that some of it was eliminated in the urine; but as soon as the colic and collæmia departed, their metabolism was again equal to the task and the glycosuria ceased.

The fall of urea shows not only that the liver is implicated in lead colic, but that all the tissues of the body are implicated and have their metabolism hindered and their combustion reduced by the all-pervading collæmia, and similar transient glycosuria no doubt similarly caused, is seen in cases of strangulated hernia, &c., F. Neugebauer (in *Wien. Klin. Wochenschrift*, September 10, 1896).

The altered urinary pigments and the subicteric tint of the conjunctiva are also very interesting, but point rather, I think, to increased blood changes and destruction of cells, which is sure to take place as another result of the collæmia (see chapter xii.), than to any special implication of the liver; though no doubt this important gland is implicated along with all the great metabolic tissues.

And this argument receives, I think, interesting confirmation from the researches of Dutournier and others, on what has been called "Bronzed Diabetes." See *British Medical Journal*, Epitome, Dec. 28, 1895, p. 101, where it is said that the above-named author "suggests that in these cases there is a decomposition of hæmoglobin, brought about by some as yet unknown cause." From my point of view the cause is well known, and the association of this slight hæmoglobinæmia with diabetes is completely explained by their being, as shown in this and the previous chapters, two results of one and the same cause, collæmia.

It follows from this reasoning that clearing the blood of uric acid will do good, while increasing the amount it holds in solution will do harm; and I have just pointed out that acids, opium, iodide of mercury, and other drugs which clear the blood of uric acid are useful, while fevers and surgical operations, which have the same effect on uric acid, are well known to diminish the output of sugar; while on the other hand alkalies, which increase the uric acid, do harm.

Acids and opium often have a similar good effect in albuminuria;

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and a fever may not only, as I have shown, diminish the dropsy, but also reduce the total output of albumen.

I shall now go on to show that salicylates which clear the blood of uric acid by effecting its elimination are also very useful in glycosuria and diabetes.

Mary A. D., age 55.—An out-patient at the Royal Hospital in January, 1888. Complains of thirst and irritation of vulva. Urine pale amber, 1020; 3·2 per cent. sugar. Alkalies and nux vomica no effect. After four weeks of salicylate, urine 1014. No sugar. Drinks much less. Salicylate left off, and in two weeks urine 1020 and 3 per cent. of sugar, and again salicylate reduced it to 1011 and no sugar.

Mrs. C., age 45.—May, 1888. Urine 1032-1040 and containing 5 per cent. sugar. Put on salicylate, and in seven days' time the urine was 1035 and 2·5 per cent. sugar. Treatment continued, and two weeks later urine dark amber, 1030, and only ·5 per cent. of sugar. Drinks much less.

I then altered her diet; left off the excess of meat she was taking, and put her on milk, fruit, and vegetables, and so long as she took the salicylate these did not increase the sugar, except on one occasion when it reached 1·6 per cent. She found that potatoes were worse than other vegetables, and produced diuresis (probably from the large amount of alkali they contain interfering with the action of the salicylate, see p. 37). She attended for many months; the sugar in spite of diet keeping about 1 per cent.

Her husband then left the district in search of work, but a year later, October, 1889, she came back asking for more of the medicine which had done her so much good. She is paler, and has wasted considerably since last seen in 1888. Urine is now 1030: contains 5·7 per cent. of sugar, urea 1·5 per cent., and uric acid ·08736 per cent., uric acid to urea 1—17, urea to sugar 1—3·8. A large excretion of uric acid, and no doubt collæmia contemporaneous with glycosuria. Fourteen days later, after a course of salicylate, the urine only contained ·6 per cent. of sugar.

November, 1890.—Returned again after considerable absence, and again salicylates reduced her sugar in a week to 2·5 per cent. She was, however, upset by home troubles, and could not take her medicine or attend regularly.

February 16, 1891.—Took her into the Royal Hospital, Waterloo Road. No drugs except a little dilute phosphoric acid, a little sal volatile for feelings of "weakness and sinking" (patient probably indulges in alcohol at home for these feelings). Urine of twenty-

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four hours 990 cc. 1046. Sugar 7·1 per cent., urea 1·6 per cent., uric acid ·06720 per cent. Uric acid to urea 1—23. Urea to sugar 1—4·4. Total sugar 2·4 oz.

On February 26, after ten days on salicylates, urine was 1335 cc. 1034, urea 1·5 per cent., sugar 3·6 per cent. Urea to sugar 1—2·4. Total sugar 1·6 oz. Salicylates had here reduced the total sugar, and had also reduced it relatively to the urea, which is perhaps the safest guide of all.

She remained in for several weeks, during which the sugar was reduced to 2 per cent. or less with the relation of urea to sugar 1—1·2. Patient, however, became unruly, dissatisfied and disobedient, possibly owing to alcohol and stimulants being cut off, and took her discharge.

During the first part of her time in hospital she was menstruating, and this appeared to increase the feelings of sinking and faintness, as it doubtless also lowered the acidity, produced increase of collæmia, and also interfered with the full action of the salicylates.

Henry F., age 54, November, 1888.—"Glycosuria and acute gout," under the care of Sir Dyce Duckworth, who very kindly allowed me to examine the urine.

Urine on two days without treatment gave 2000 and 1650 cc. Uric acid to urea 1—48 and 1—33. Urea to sugar 1—6·2 and 1—5·9.

There was here a minus excretion of uric acid with glycosuria, but no doubt when the uric acid has produced the condition which gives rise to glycosuria, this may go on for a day or two when there is no collæmia; besides the fact that the relation on the twenty-four hours was 1—48 and 1—33, is no proof that there was not some collæmia for several hours during the alkaline tide of each day.

After three days on salicylate the total sugar was less by 200 grs. than at first, and the relation of urea to sugar was 1—4·8.

But the patient was now up and free from his gout, so the examination could not be carried further. The notes of his case do not say whether he had the glycosuria along with the acute gout or not. He continued to take salicylate for some time, as he said it did him good; but he also indulged freely in beer and brandy, and this latter would no doubt aid the uric acid in producing congestion of the liver.

Jane B., age 33, November, 1888.—Complains of weakness and languor; drinks all day long and passes much water, especially during last two months. She first noticed excessive thirst about

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eighteen months ago, the time of commencement of her last pregnancy. Urine pale amber, 1043, urea ·6 per cent., uric acid ·02016 per cent., sugar 10 per cent. Uric acid to urea 1—30, urea to sugar 1—17. She was given some instructions about diet and put on alkalies and nux vomica. These did no good, and at the end of a week sugar was still 10 per cent. Dec. 1, she was put on salicylate, and told to try and estimate amount of water in twenty-four hours.

Dec. 8.—Urine 1040 ; sugar 9 per cent.

Dec. 16.—Passed twenty pints of urine yesterday ; thinks she has passed considerably more than this. Urine 1042. Sugar 8 per cent. Urea to sugar 1—12.

After this sugar fell steadily to 7 per cent., with relation to urea 1—8·7, and she began to gain weight and get more colour.

In April, 1889, during my absence salicylate was stopped and nux vomica and alkalies repeated; the mixture made her worse, and she threw it away after two or three doses. (It is a remarkable fact that nearly all these patients with glycosuria or diabetes say that alkalies make them worse and acids make them feel better. The former increases, but the latter diminishes collæmia.)

She did not come again till Aug. 17, when she was obviously worse—pale, feeble, and with quick pulse. No urine brought; given salicylate again.

Aug. 24, 1889.—Better, and less thirst: when thirst is great nothing under two pints of water is any use. Urine to-day 1040, sugar 10 per cent.

In September urine had fallen to ten pints a day, sugar 6 per cent., and urea to sugar 1—6; and at the end of this month sugar was 5·5 per cent., and urea to sugar 1—5·5.

In October, sugar 5 per cent., and urea to sugar 1—5, and she got on so well that she refused to leave her children and come into hospital.

The urine was reduced to less than one-half of the original amount, and the percentage of sugar to one-half also, so that the total sugar was reduced to one-fourth of the original quantity, and the relation of urea to sugar altered from 1—17 to 1—5.

She improved and felt better in every way while taking the salicylate, and while the sugar was diminishing she steadily increased in weight.

She continued to attend for many months after this, and so long as she took the salicylate did well. I found that small doses of morphine increased its effect, and gave her for some time gr. $\frac{1}{8}$ in

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pill three times a day. By this means sugar was reduced to 4·5 per cent., and on one occasion to 3·5 per cent. But unfortunately, in the spring of 1890 there was a change: she again became pregnant, and this produced a considerable amount of vomiting; this interfered with the taking and action of the salicylate, and she went rapidly down hill. She still obstinately refused to come in, and soon ceased to attend. My last note is dated Oct. 7, 1890, when she was much weaker and worse, and salicylate had been left off for some time and bismuth and other treatment of symptoms made use of. As she refused to come in, in spite of all I could say, nothing more could be done, and I fear that she soon died.

The case, however, illustrates well the power of salicylates in what no one probably will deny was severe diabetes; and I have no doubt that the drug prolonged her life by at least two years, as when I first saw her I did not expect her to live a month, and but for her unfortunately again becoming pregnant (which is in itself strong testimony to the improvement in her condition), still better results might have been obtained.

With regard to this patient's history and the fact that her diabetes probably originated in a pregnancy, we have seen that in her last pregnancy she had considerable vomiting and then got much worse, and I think it is probable that in her former pregnancy there was vomiting also, and the diabetes thus originated in the severe collæmia so produced. In this case almost every word written in the last chapter with regard to the causation of albuminuria in pregnancy would apply equally well to the causation of this glycosuria and diabetes: only in the one case the defective combustion affected the starches and sugars, in the other the albumens, and in some intermediate cases as we know it may affect both, or now one and now the other alternately. I think it is not too much to say that if this patient had had normal pregnancies free from vomiting she might have been alive still and possibly never have had diabetes.

Another case is that of Winifred H. F., age 8 years, who was admitted under my care at the Royal Hospital for Children and Women, January 22, 1891.

Complained of thirst and nocturnal urination; pale, wasted; weight 2 st. 5 lbs. Some increase of liver dulness, and constipation.

Urine 2220 cc. pale amber, 1040. Sugar 5·5 per cent., uric acid to urea 1—33. (No excess of uric acid [?] due to phosphoric acid given as a drink.) Urea to sugar 1—5·5, urea per lb. 10·3 grs. She was put on diet; no drugs except a little dil. phosphoric acid.

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The sugar fell to 5 per cent. and then to 4·1 per cent., but urea fell very considerably also, and on February 9 it was only 4·6 grs. to lb. Diet here was interfering seriously with nutrition, and though sugar fell, urea fell more; very different from what had occurred in the previous case with salicylate.

She was given some salicylate, but it unfortunately upset the stomach and made the failure of nutrition greater; sugar and urea both falling considerably. Her pulse on several occasions was relatively slow, showed considerable high tension and occasional intermissions.

The salicylate was therefore stopped, and she was given two pints of milk and some brandy. She had previously been taking food (diabetic diet) badly: but she liked the milk and began to improve on it, and urea and sugar both increased.

February 12.—When urea got back to 9 or 10 grs. per lb. and sugar to 5 per cent. salicylate was again given in small, slowly increasing doses. Both urea and sugar, however, continued to increase, though on February 18 urea was to sugar 1—3·2, and on the 19th 1—3, and on the 21st 1 to 2·9, and on 24th 1 to 2·3.

Salicylates now apparently caused some dyspepsia and diarrhœa, and all drugs were therefore stopped, and on February 28 urea was to sugar 1—3·3. It looked, therefore, as if the salicylate had had some effect in lessening the sugar relatively to the urea.

March 2.—Slight rise of temperature, and sugar fell in consequence, the urea relation being 1—2·2.

Salicylate was begun again, gr. vii. four times a day, but again diarrhœa followed its use and some tr. opii was given.

March 4.—Urea to sugar 1—3·1; salicylate had not begun to act.

March 5.—1—3.

March 7.—1—2·3.

March 12.—Opium stopped. Given codeina gr. ¼ three times a day, and salicylate gr. x. four times a day, urea to sugar 1—2·2.

March 18.—Rather more languid. Codeina stopped and liq. morph. hydroch. ♏x. given four times a day with the salicylate.

March 26.—Going on much the same, but there is occasionally some vomiting, and the diarrhœa has not completely ceased. Urea to sugar 1—2·2. Total urea 739 grs. or 22 grs. per lb. She is now taking a considerable quantity of milk and is not kept on strict diabetic diet, as it was found that she took this badly, urea diminished, and she got into a lethargic condition, which disappeared as the diet was improved.

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March 27.—Some diarrhœa again, so salicylate and morphine stopped.

March 31.—No diarrhœa or vomiting; given codeina gr. ½ three times a day.

April 4.—On codeina; temperature raised to 101°. Takes badly and has some nausea: urea to sugar 1—2·5 (effect of fever), but urea has fallen to 540 grs., 16 grs. per pound.

April 6.—Not so well; very drowsy, especially in the morning after breakfast, when she falls asleep and does not wake for several hours. Takes badly, some nausea. All drugs stopped, milk increased to three pints, brandy 2 ozs.

April 9.—Better and brighter much; takes better, but urine has increased in quantity and specific gravity. Salicylate and morphine mixture repeated.

She died on April 19 (while I was away for a holiday) with some symptoms of diphtheria, and another child in the ward had a suspicious throat and was isolated.

Permission for a *post-mortem* examination could not be obtained, so the exact nature of the case remains in doubt. There was no optic neuritis, and such vomiting as occurred seemed to be the result of drugs rather than of any central cause. The only physical sign was a moderately well-marked increase of liver dulness.

As to drugs, the salicyates on several occasions reduced the sugar relatively to the urea, and that without in any way reducing the urea.

The codeina diminished urea and sugar, but did not diminish the sugar relatively so much as the salicylate. On one occasion it appeared to cause drowsiness.

Diabetic diet was an absolute failure, causing a great fall of urea and producing a lethargic condition which would no doubt have been fatal if the diet had not been improved; possibly diet was begun too suddenly. This is in complete accord with the observation of Hirschfeld (*Deutsch. Med. Woch.*, June 27, 1895), that inanition is the cause of the coma in diabetes; and my own observation decidedly leads me to agree with him, for I have in several other cases noted the approach of such conditions along with a marked fall in urea, and if I could run up the urea I appeared to be able to ward off the coma. In such cases it is obviously of the greatest importance to examine the urea; anything that interferes with the taking and digestion of food will reduce both sugar and urea, but this is not a curative action. Salicylate reduced the sugar relatively to the urea, and the child fully held her own while taking it. Un-

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fortunately, however, it appeared to produce some nausea and diarrhœa.

I shall also give the notes of a case in which salicylates given along with small doses of calomel eventually acted well, though at first they appeared to fail.

W. H., age 36. Admitted under my care in the Metropolitan Hospital, January 18, 1893. Complains of increase of appetite one month, and increase of thirst two weeks.

His father is alive and well, but suffers from lumbago and piles occasionally.

His mother has "rheumatics" in the hands. He has five sisters, who are well.

Patient has not had any fevers, not even the influenza.

His tongue is slightly red at the tip and edges, but not specially clean.

His bowels are constipated.

There are no physical signs.

January 19.—Weight, 92 lbs. 10 ozs. Put on a modified diet, gluten bread. Milk Oii., and imperial drink without sugar. No potatoes, bread or sugar.

January 22.—Urine, 74 ozs.; sp. gr. 1035. Acid. No albumen. Sugar, 3·1 % = 1059 grs.; urea, 2·4 % = 819 grs.; relation, 1—1·2.

January 24. Bowels opened by mist. sennæ co. Thirst is rather less.

January 28.—Sodii salicyl. gr. xv. Out of aq. menth. pip., given every six hours. Weight 103 lbs.

February 1.—Urine, 58ozs.; sp. gr., 1036; sugar, 3·1 % = 890 grs.; urea, 2·6 = 696 grs.; relation, 1—1·11.

The salicylate appears to cause some nausea, and he is not taking his food so well. Try to take the salicylate in powder.

February 4.—Urine, 56 ozs.; sugar, 1·4 % = 361 grs.; urea, 2·4 % = 620 grs.; relation, 1—0·58. Weight, 103 lbs. 8 ozs.

Appetite still bad, so salicylate was stopped and iodide of sodium, gr. vii., given in place of it three times a day.

Here we see again that the sugar has fallen greatly down to almost one-third of the amount on January 22, but urea has also fallen by as much as 200 grains, and we know that this was due to deficient income of food from nausea and loss of appetite, and if we add, say 200 grs. to the sugar on this account, the relation would come out nearly 1—1, or close to what it was on February 1.

February 8.—Urine, 98 ozs.; urea, 2·1 % = 950 grs.; sugar, 2·0 = 905 grs.; relation, 1—0·95. Iodide increased to gr. x.

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February 10.—Urine, 80 ozs.; urea, 2·4 % = 837 grs. sugar, 3·1 % = 1,145 grs.; relation, 1—1·2. Weight, 103 lbs. 8 ozs.

February 14.—Iodide left off, and salicylate again given in different form.

February 15.—Urine, 90 ozs.; urea, 2·4 % = 997 grs.; sugar, 3·3 % = 1,372 grs.; relation, 1—1·3.

February 18.—Urine, 94 ozs.; sp. gr., 1037; urea, 2·7 % = 1,130 grs.; sugar, 2·6 % = 1,088 grs.; relation, 1—·96. Weight, 105 lbs. 6 ozs.

February 22.—Urine, 86 ozs.; sp. gr., 1031; urea, 2·3 % =913 grs.; sugar, 2·5 % = 993 grs.; relation, 1—1 (nearly).

February 25.—Urine, 102 ozs.; sp. gr., 1036; urea, 2·3 % = 1,802 grs.; sugar, 2·9 % = 1,365 grs.; relation, 1—1·2. Weight, 106 lbs.

Here again, though the salicylate at first reduced the sugar relatively to urea, the improvement was not maintained.

Liq. morph. hydrochlor. ♏ xii. was added to each dose of the mixture.

March 1.—Urine, 46 ozs.; urea, 2·7 % = 572 grs.; sugar, 1·2 % = 254 grs.; relation, 1—·44. Weight, 106 lbs. 4 ozs.

Here again, a great diminution of sugar, but also a great fall of urea, and no doubt the salicylate and the morphine upset appetite and digestion and accounted for this.

March 8.—Urine, 71 ozs.; sp., gr., 1032; urea, 2·0 % =710 grs.; sugar, 2 % = 710 grs.; relation, 1—1.

March 10.—Urine, 78 ozs.; sp. gr., 1024; urea, 2·2 % = 791 grs.; sugar, ·8 % = 287 grs.; relation, 1—·36. Weight, 106 lbs. 8 ozs.

Here is some improvement, and, as urea is rising, it is probably due to the drugs.

March 14.—Urine, 64 ozs.; sp. gr., 1025; urea, 2·7 % = 797 grs.; sugar, ·5 % = 147 grs.; relation, 1—·19. Allowed a small bit of toasted bread twice a day.

March 17.—Urine, 70 ozs.; sp. gr., 1023; urea, 2·4 % = 776 grs.; sugar, ·75 % = 241 grs.; relation, 1—·3. Weight, 107 lbs. 4 ozs.

March 24.—Weight, 108 lbs. 8 ozs.

March 29.—Urine, 74 ozs.; sp. gr., 1036; urea, 2·4 % = 751 grs.; sugar, 3·3 % = 1,127 grs.; relation, 1—1·5.

Toast was left off and liquor pancreaticus given, also calomel gr. ½ twice daily.

April 1.—Urine 62 ozs.; urea, 2·7 % = 773 grs.; sugar, 2·5 % = 716 grs.; relation, 1—·9; weight, 106 lbs.

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April 11.—Has had vomiting in the morning since 6th. Urine, 44 ozs.; urea, 3·5 % = 711 grs.; sugar, 5 % 101 grs.; relation 1—·14.

April 14.—Weight, 108 lbs.

April 19.—Urine, 54 ozs.; sp. gr., 1026; urea, 3·3 % = 822 grs.; sugar, ·7 % = 174 grs.; relation, 1—·21.

April 22.—Has had some pain in connection with the sac of a femoral hernia; but this has now been relieved by rest and ice locally. Urine, 52 ozs.; sp. gr., 1021; urea, 2·1 % = 508 grs.; sugar, ·15 = 20 grs.; relation, 1—·03.

April 26.—Urine, 44 ozs., high colour; sp. gr., 1030; urea, 3·8 % = 671 grs.; sugar, ·4 % = 81 grs.; relation, 1—·1; weight, 104 lbs. 12 ozs.; given claret, ozs. ii.

April 29.—Urine, 64 ozs.; sp. gr. 1019; urea, 2 % = 591 grs.; sugar, ·1 % = 56 grs.; relation, 1—·09.

May 3.—Urine, 38 ozs.; sp. gr., 1030; urea, 3·4 % = 595 grs.; sugar, ·03 % = ? *nil*.

Here sugar is reduced to *nil*, though urea is as high as at last note. Toast allowed again.

Is still on salicylate, morphine, calomel, and liq. pancreaticus.

May 6.—Urine, 48 ozs.; sp. gr., 1029; urea, 3·2 % = 708 grs.; sugar, none; weight, 104 lbs.; liq. pancreaticus left off.

May 10.—Quantity and sp. gr. as at last note; still no sugar.

May 13.—Weight, 106 lbs.

May 19.—As sugar continued to be absent and he was going on well, he was allowed to go out, taking the salicylate mixture and calomel with him.

August.—Attends at the hospital every few weeks and continues the mixture and the calomel powders. Sugar remains absent, and he is quite holding his own.

I think the credit of this improvement remains with the salicylate and calomel; the liq. pancreaticus appeared to have no effect whatever; the salicylate and morphine also appeared to account for an improvement in March.

As mentioned in a previous case, morphine helps the action of a salicylate, and I believe that it may do this by keeping up the acidity, and preventing any of the uric acid, which salicylates bring through the blood, from getting into combination with an alkali, because it is the combination of uric acid with an alkali which affects the vessels and does all the harm.

And my object in giving calomel was just the same, namely, to keep the blood clear of uric acid combined with an alkali; and

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calomel does this by directly combining with the uric acid (see p. 60), and it appears from the results in this case, that it helps the action of the salicylate more than the morphine does, possibly because its effect is independent of acidity; and under certain conditions the morphine may not be able to raise the acidity (see p. 54).

Considering that in this case there was only 3·1 per cent. of sugar to begin with (though, by the way, this was on diet), I should have expected a more decisive result with salicylates alone; but their partial failure was, I think, largely due to their being taken badly, and producing nausea: when they do this they are no use in any case. They are also no use when there is nausea or vomiting from other causes (see Case of Jane B.). I believe because there is then so much alkali in the blood, that a good deal of the uric acid is sure to combine with it.

Still, I consider that given along with acids or small doses of morphine or calomel, the salicylates are the most useful drugs we possess for the treatment of these troubles, and they act by eliminating uric acid, and so clearing the blood of it. I have often seen the sugar greatly reduced by opium or codeine, but they have also appeared to me to reduce urea very considerably at the same time, while with the best action of the salicylates urea rises.

Frerichs says that salicylates reduce sugar by interfering with digestion; but in several of my cases salicylates not only greatly reduced the sugar without reducing urea, but the patients steadily gained weight while taking them.

In my paper on the use of salicylates in diabetes I mentioned that two cases had been reported as cured by them, and since my paper, I have heard from others who have followed up my suggestions and used them with great benefit (see Dr. Mansel Sympson, *Practitioner*, August, 1891), and Dr. Brooks, of Lincoln, read a paper before the Lincoln Medical Society in 1891, on the use of salicylates in diabetes.

In suggesting that glycosuria and diabetes may be due to a failure of combustion and a slackening of metabolism, which, again, may result from the vascular effects of uric acid, pointed out in previous chapters, I am very far from claiming that all such cases are due to uric acid.

I believe, however, that the connection between gout and diabetes is both wider and deeper than has hitherto been suspected; and that some of the riddles of this sphinx (Frerichs, "uber den diabetes," p. 275), may be solved by admitting provisionally the power

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of uric acid over metabolism; and by thus admitting it provisionally, we are by no means bound to forego any opportunity that may offer of putting the point to the most careful test we can devise.

And the more careful and complete our tests the more evident will it become that glycæmia, glycosuria, and not a few cases of diabetes are really due to a failure in the metabolism and combustion of carbo-hydrates, just as hetero-albuminæmia and albuminuria are due to a similar failure in the combustion of albumens, and that the action of uric acid on the circulation is amply sufficient to account for failure of combustion in both cases, and so for the fact that both may occur in the same individual (see p. 473.)

Then, as pointed out in an article mentioned in the *British Medical Journal*, Epitome, 1896, vol. 2, p. 97, and January, 1897, p. 5 of Epitome, there may be occasional excretions of a little sugar for years before there is true diabetes. And this is the exact parallel of what we see in migraine, when there is often occasional albuminuria for years before Bright's disease, and constant albuminuria supervene; and this reminds me that I have at present under my care a case in which periodical migraine of many years standing has ended, not as is usual in albuminuria and Bright's disease, but in glycosuria and diabetes.

It seems then that there is here between these two diseases, albuminuria and Bright's disease on the one hand, and glycosuria and diabetes on the other, a most extensive parallelism—one might almost say identity—and one cannot help feeling that just as in the cases of headache and epilepsy previously mentioned, there must exist below this parallelism its one possible cause—community or identity of causation.

And this common factor, the cause of both diseases, is defective circulation, bringing about defective combustion, and we now see that the best and most complete explanation of the defective circulation is capillary obstruction by uric acid collæmia.

There are also some indications that while the defective combustion thus produced may affect either albumens or sugars, or first one and then the other, its actual effect in any given case depends on associated conditions.

When the stress of the defective circulation, as determined by other concomitant conditions, such as cold and damp, falls on the skin, we are likely to get albuminuria and Bright's disease; and when it falls specially on the liver and chylopoietic viscera, then glycosuria and diabetes is the more likely result.

Cases which are still functional will respond most decidedly to

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the treatment of the uric acid factor; while those which have become organic, owing to changes in the metabolic tissues, will be affected only to a certain extent; and those which are from the beginning organic and due to lesions of the great nerve centres, will hardly respond at all to the treatment of uric acid.

The indications for the treatment of such a glycosuria or diabetes are to diminish the introduction and formation of uric acid, and to clear out that which has accumulated in the body. A long course of salicylates will satisfy the last indication; and if they, at the same time, remove the sugar, we ought, I think, to go gradually back to ordinary diet, and even beyond it; eventually reducing animal food to small quantities of milk and cheese; and, unless we are able to do this, I believe that relapse is often merely a question of time.

As I have said, I believe that the large amount of meat commonly given in diabetes acts as a stimulant, and therefore just like opium or mercury keeps the blood clear of uric acid for a time: but like these drugs it can only do good for a short time while the stimulation lasts, as it not only does not clear the uric acid out of the body, but on the contrary (and in this respect it is worse than the above drugs) it steadily pours into it a considerable quantity of this substance day by day.

Whether this great excess of uric acid has anything to do with the coma that often ends the disease, may be doubtful, and I have already made some observations on this point on p. 503, showing that in the opinion of myself and others, the coma was due to inanition: but I am not at all sure looking to the terrible effects of uric acid on nutrition and combustion that the inanition in its turn may not be due to uric acid collæmia; and this would fit in very well with the fact observed on p. 503, that a rise of urea which entails a corresponding rise of acidity generally suffices to clear off the coma. And I shall have to refer again in the following chapters to the evil effects of a pure meat diet when given for chronic arthritis, and in one of the cases there mentioned, the patient was insensible for some thirty-six hours.

But be this as it may, I would make this practical suggestion that probably the only way out of diabetes is to clear the body and blood of uric acid, and that it is quite impossible to do this while an almost pure meat diet is pouring in the xanthins in large quantity every day.

Is it then possible to put a diabetic patient on a uric acid free diet? I have for years been attempting to do this, and now at last I see what I think is a gleam of light above the dark horizon of failure.

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In many cases I have attempted to give milk, but when the disease is at all severe, it is necessary to clear it of all sugar, and this I have tried to do, with more or less success, by coagulating it with rennet and then carefully washing the curds free from the whey which contains most of the sugar: but I believe there has now been invented a process by which the albumens of milk can be obtained in practically complete separation from the sugar and other constituents, and I shall mention this further in the chapter on treatment.

Then if this is so, we find ourselves at once in a stronger position with regard to the treatment of diabetes, for we have two forms of albumen which can take the place of animal flesh, and which will probably introduce no uric acid on xanthin into the body.

The other form of available albumen is one already in use, namely gluten, but this again might, I believe, be used much more extensively than at present.

What we have to aim at then is to stop the introduction of xanthins by substituting milk albumens and gluten for animal flesh, and then continue the clearing out of uric acid by means of the salicylates as before, and if both diet and drugs succeed, we shall have what we have never yet had in this disease, a real chance of success.

I could easily give notes of further cases, but they do not show anything not also shown by the above cases.

And these show, I think, that in a considerable number of cases of diabetes, a course of salicylates with the help of opium or calomel will decidedly reduce the output of sugar, and check the progress of the disease, and that where they fail it is doubtful whether anything else will succeed.

Opium and codeina seem to me to labour under the fatal objection that they often interfere with appetite and cause a fall of urea as well as of sugar.

They cure also, if my pathology is correct, merely by clearing the blood of uric acid, and as no provision is made for its elimination, this is almost certain to be followed sooner or later by a rebound, with serious or fatal effects.

So far as I have been able to watch the use of opium and codeina by others, they have not presented any advantages over salicylates, and have often appeared to me to fail in prolonging life as much as the salicylates might reasonably have been expected to do.

I have never cured a case of diabetes, but I believe that if cure is to be effected it will be by using salicylates and altering the diet in the direction mentioned above when they are acting well.

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W. H. died quite recently under my care, his disease having thus lasted more than four years.

In the intervals he had tried several hospitals and as many physicians, and he told me that nothing had done him so much good as salicylates with small quantities of opium or calomel.

When he returned to me this time his case was quite hopeless, as he had wasted very much during the last few months, and had several bedsores, showing most feeble nutrition; and he had also some consolidation at the apex of one lung, and a troublesome cough.

Here all drugs quite failed to produce an effect, and as in the corresponding stage of Bright's disease the fires were so low and the tissues so wasted that it was impossible to stimulate them again.

Dr. S. West published in the *British Medical Journal*, August 24, 1895, his experiences of the treatment of diabetes mellitus by uranium nitrate, which he thinks may act by checking the rapid digestion of starch and some forms of albumen.

I have made a few experiments with this drug, and the results show very clearly the way in which it acts.

It causes a distinct rise of acidity and a diminished excretion of uric acid with well being and diuresis, and these effects are so marked that quite small doses suffice to demonstrate them.

Thus on a day when no drugs were taken, urinary water was 1520 cc., acidity 57·4 grs., and the relation of uric acid to urea 1—27.

On the following day gr. iii. of uranium nitrate were taken three times a day after meals.

This produced marked mental and bodily well being, the urinary water rose to 1860 cc., and the acidity to 61·2 grs., and the relation of uric acid to urea was 1—38.

I think, therefore, that there can be no doubt that nitrate of uranium clears the blood of uric acid and increases metabolism and combustion; and like many of the drugs mentioned above diminishes the excretion of sugar in diabetes, because it increases the combustion. I may say that I have had a patient under my care on uranium nitrate for more than 18 months; she is a somewhat similar case to W. H., and is at present holding her own, though the dose of the drug has had (as one would expect) to be steadily increased; but this is obviously prolongation of life, not cure.

Calcium is another drug which taken in the form of powdered egg-shell has been credited with curing or relieving diabetes, and from what has been said of the effects of calcium salts on p. 53 it is clear that it may also, like the uranium salt, clear the blood of uric acid and improve combustion.

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CHAPTER XV.

Gout.

Since I first discovered that in driving uric acid out of the blood while curing an attack of headache or mental depression, I produced pricking and shooting pains in the joints, the explanation of the arthritis of gout has never seemed to me to be a very difficult matter.

And it still seems to me that when we have obtained a complete knowledge of the chemistry and solubility of uric acid under the conditions present in the human body, we shall have no difficulty in explaining completely all the phenomena of gout.

I am quite prepared to undertake to produce a uric acid arthritis in anyone provided my instructions are carried out, but the clinical result will often resemble what is described as the arthritis of rheumatism rather than that of gout.

From my point of view the arthritis in both diseases is due to uric acid, which, in acute rheumatism, is suddenly driven into a large number of joints, where, however, it remains generally only for a short time, and is then completely removed; but in gout a great part of the uric acid in the blood is (generally by the action of some external causes) concentrated on one particular joint where it is not only present in greater quantity, but remains longer than in the case of acute rheumatism.

I believe, however, that it is quite possible by imitating nature to produce at pleasure an arthritis which would be called rheumatism, or one which would be pronounced gout, by those who did not know how it was produced.

If, in the arthritis called rheumatism, the uric acid is removed in the course of a few days, only microscopic lesions are produced, which are quickly repaired, and leave no trace after death, but if injury, cold, or other external causes prevent the removal of the urates from one or more of the joints, they may set up and maintain an irritation in its fibrous structures which may obtain a con-

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siderable hold on the tissues and go on smouldering by itself after the uric acid has been removed. In this way are brought about extensive lesions of structure which even after acute rheumatism are sometimes visible after death, and where uric acid has been again and again precipitated (from causes I shall presently speak of) on the irritated areas, changes commonly called rheumatoid are at length produced.

These rheumatoid changes, when extensive, should be regarded as in part the direct effects of the irritant uric acid, and in part due to the smouldering on of the irritation it causes, so that I have been accustomed to speak of the uric acid as the fire, and the rheumatoid changes as the ruins, and obviously the treatment of the ruins is a very different matter from that of the fire. To remove the uric acid is the best treatment of the fire, but that will not rebuild the ruins.

I was interested to see that in his address in the section for diseases of children at Bournemouth, Dr. Goodhart speaks very strongly as to the relationship of gout and rheumatism. Thus (*British Medical Journal*, 1891, vol. ii., p. 252) he is reported as saying: "In the first place I hold that gout in children is not to be discriminated from acute rheumatism," and further on he says: "I think that in summing up what gout is we must say that under some circumstances, or at one period of its life, gout is acute rheumatism."

I have shown that under all circumstances and at all periods gout is rheumatism and rheumatism gout, and that while both are due to uric acid the clinical picture varies with age and other factors, the action of which can be completely explained, but I am glad to see so great an authority as Dr. Goodhart arriving at the same conclusion from different premises.

Then again, I note that Mr. Jonathan Hutchinson says (*Trans. of International Med. Cong.*, 1881, p. 92) that rheumatism and gout occur in the same families, and the one is as much hereditary as the other; and he also says, "Thousands of specimens will be found in museums showing rheumatism only, but of those which show gout (lithate deposits) there are but few which do not show some traces of the changes characteristic of rheumatism" (p. 96); and on the same page he remarks that "rheumatoid arthritis is seen in children as the result of descent from gouty parents; also a special form of iritis, especially seen in those who inherit also proneness to chilblains." There is no lithate deposit in such cases, but later on, especially if disease of kidneys comes on, then they get urate deposit.

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It is necessary to make these preliminary remarks, or the position I shall take in this and the following chapter would not be understood.

What evidence have we that uric acid produces such irritation as that I am speaking of in the fibrous structures?

I have often quoted Sir A. Garrod's remarks on the effects of wines, &c., and have suggested that it was the acid in these beverages that drove the urate into the joint and produced the inflammation, of which the pricking pain is the sign; he says (p. 245), "Where a few glasses of wine, ale, or porter quickly and invariably produce in any individual an inflammatory affection of a joint, such inflammation is of a truly gouty character;" and in the lines preceding this he mentions how some sufferers have heat, throbbing, stiffness, and pain in their gouty joint after two glasses of port or a single glass of champagne. Now it is easy to demonstrate that champagne is intensely acid—more so than the other wines and malt liquors mentioned, and Dr. Brunton (in the debate on my paper on "Salicylates and Rheumatism," *Proceedings of the Royal Medical and Chirurgical Society*, April, 1890, p. 109) mentioned a case in which champagne had apparently produced symptoms of poisoning by its great acidity.

There can then, I think, be no doubt that these beverages acted as doses more or less strong of acid, and drove the uric acid out of the blood into the already irritated joint,and for the effects of sherry on the acidity of the urine see fig. 54; but all these things can be easily shown to affect, not only the acidity of the urine, but the excretion of uric acid, and the condition of the blood itself, as shown in fig. 45.

Then, as mentioned by Sir W. Roberts, in the above debate, Ebstein has shown that urate dissolved in phosphate of soda produces irritation and morbid change when injected into the cornea, while the phosphate alone produces none.

Then again, Sir A. Garrod has pointed out (previous reference, p. 292), that the cartilages and fibrous tissues of joints have but little vascularity, and are less alkaline than other tissues, or than the blood, and if this is so we can easily see why urates should become "less soluble and more easily retained" (to quote Sir A. Garrod's words) in the neighbourhood of joints.

Further, the joints in the old are probably both less vascular and less alkaline than those of the young, so that such external causes as injury or cold will more easily diminish their alkalinity in the old, and produce a local concentration of urate and a gouty arthritis.

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In the young, on the other hand, the effects of local cold or injury will be less, the alkalinity will be better maintained, and it will only be when general causes act all over the body, such as severe chill and wetting during perspiration, that the alkalinity of all the joints will be reduced at once, and the more general arthritis of acute rheumatism will result. Hence the joint irritation produced by urates tends to be general and acute in the young (acute rheumatism), local and subacute or chronic in the old (gout).

With regard to the action of acids, I have produced pricking and shooting pains in my own joints—many scores of times, when using them to remove the uric acid headache or mental depression (see also remarks on fig. 54), and in a case of gout under the care of Sir Dyce Duckworth in St. Bartholomew's Hospital, where he kindly allowed me to examine the urine, I was able to show (*St. Bart. Hosp. Reports*, vol. xxiv., p. 217) that every time the acidity rose the uric acid fell below the urea (relation 1—45 or 1—50, a great retention of uric acid), the temperature tended upwards and the pains increased and became severe, and conversely whenever the uric acid was above urea (relation 1—24, excretion in excess of formation)—whether this result was produced by salicylates or alkalies—the pains diminished or ceased, and the temperature subsided. I hope that anyone who is still sceptical about the effects of acids in gout will look at the curves given in the above paper, and will then try acids on themselves, or any gouty patient who will consent to the experiment, and I am confident that the results will remove all doubts, and for a similar observation in an attack of gout, see clinical note by Dr. Lyddell, *Lancet*, 1893, vol. ii., p. 631.

In reference to physiological relations I would point out that the attack of gout commonly occurs at night during the acid tide, when the excretion of uric acid is at its lowest, and during the course of the attack the pains are always worst and the temperature highest at night. The curves in my paper above referred to show this well. Sir A. Garrod (previous reference, p. 42) quotes from Sydenham's description of the attack in which the hour of onset is mentioned as 2 a.m., and on p. 44, still quoting from the same authority, we find this statement: "One thing, however, is constant—the pain increases at night and abates in the morning." I hope that no one who has followed my reasoning will have any difficulty in understanding the meaning of this. It is in absolute accord with my statement, that the excretion of uric acid is inversely as the acidity, and that when uric acid fails to be excreted, it is retained in the joints and irritates them.

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As regards season, Sydenham's account is equally emphatic. He says (p. 42): "Towards the end of January or the beginning of February suddenly and with scarcely any premonitory feelings the disease breaks out." That is to say, at the very coldest season of the whole year, when, as I have shown, the acidity is highest and the excretion of uric acid least (see p. 27).

But indeed, the whole of Sydenham's description can be easily explained in terms of uric acid excretion by anyone who is conversant with it. Thus he says (same reference, p. 42): "But a few days before this (that is the attack) torpor comes on and a feeling of flatus along the legs and thighs." This means a slight fall in acidity (no doubt due to the stomach derangement he speaks of as a forerunner of the attack) and a plus excretion of uric acid, and its excess in the blood causing "torpor," or as I have described it, mental, metabolic and general depression. Then see what happens; he goes on: "Besides this there is a spasmodic affection, whilst the day before the fit the appetite is unnaturally hearty. The victim goes to bed in good health and sleeps," and at 2 a.m. is roused by the pain.

We have seen that there was dyspepsia with fall of acidity and collæmia with "torpor" as its sign. Then the stomach improves: the appetite is unnaturally hearty." Up go urea and acidity at a time when the blood is highly charged with uric acid, and the natural result is that it is driven into the joints, and this occurs just at an hour when the acidity has been rising for some time and is nearly at its highest point.

We can now see all our factors quite clearly, almost as well as if we had produced the attack ourselves. (1) Dyspepsia producing a fall of acidity and collæmia. (2) Improvement of digestion and appetite raising acidity and driving the uric acid out of the blood into the joints. Can anything be more simple? and this sequence can be imitated at pleasure to any required extent. But it is only by acting on a natural or artificially produced collæmia that arthritis can be caused; when there is no uric acid in the blood we cannot drive it into the joints: hence as we shall see all treatments by drugs, salts (sulphates, etc.), mineral waters, or pure meat diet which stimulate nutrition and combustion, and keep the blood free of uric acid for a time by doing so, do for such time also keep off arthritis; and conversely the worst conditions for chronic arthritis are those where joints are already irritated, and a constant supply of urates in the blood keeps up the irritation.

In connection with this causation of arthritis, I was much

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interested to hear Dr. Oliver, of Harrogate, say at a meeting of the British Balneological and Climatological Society in April, 1896, that in olden times he had often seen gout flare up in patients coming to Harrogate, as it was then the custom to put them in hot immersion baths, and these seemed to develop the gout attacks: and I hear from Dr. D'Oyly Grange, of Harrogate, that some patients still have acute gout on first coming there, and this is, no doubt, due to the salts and sulphur in the Harrogate water; but if a gouty patient is put in a hot bath, which acting like a Turkish bath (in fig. 63), is sure to flood his blood with uric acid, then the Harrogate water will be almost certain to produce an attack of gout.

Why does gout come in January and February? (1) Because during part of November, the whole of December, and January the weather is cold. This diminishes the excretion of acids in perspiration, and keeps the acidity of the urine high (Sir A. Garrod) and the alkalinity of the blood low, hence, during this period, the excretion of uric acid falls short of its formation and introduction, and it is retained and accumulated in the body (see fig. 4). (2) When, at the end of January, dyspepsia lowers the acidity for a day or two, there is a large store of uric acid in the body which is at once washed out into the blood, producing intense collæmia with "torpor" as its sign. (3) On this supervenes a sharp rise of acidity which quickly clears the blood of uric acid, driving it into the joints. (4) During the "good health" of the day before the attack the patient has probably taken a little extra exercise as well as a little extra food, and during the exercise he has produced a little warmth and diminished alkalinity in some of the joints of his feet. This has not subsided when the rising acidity of night not only prevents its fall, but increases it. Hence, at 2 a.m., certain joints in the feet are the least alkaline structures in the body, and the whole, or nearly the whole, of the uric acid in the blood is concentrated upon them, and acute pain and inflammation result.

The whole thing is a fluctuation in the excretion of uric acid, which, as I have said, can be imitated to any required extent.

In experimental work a gout attack can be produced by acids or any drugs which directly or indirectly raise the acidity or otherwise interfere with the solubility of uric acid.

But these drugs will not produce an attack unless there is plenty of uric acid in the blood for them to act upon, so that the mere fact that an acid or a dose of mercury, nux vomica, etc., has been taken without producing any pains proves nothing.

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If you are going to produce an experimental arthritis you must first bring a lot of uric acid into the blood in solution probably with a salt of potash or soda, and then administer some of the drugs which will interfere with its solubility and drive it into the joints and fibrous tissues; this is what invariably occurs in nature or an attack of gout or rheumatism does not result. A rise of acidity or the taking of a drug which causes retention when the blood is already free from uric acid naturally produces no result.

From what has been said, it must be obvious that an acid may fail to produce an attack of gout for several reasons. (1) It may fail to be absorbed from gastric irritability (nausea, vomiting, etc.), or it may irritate the stomach, and prevent its own absorption and that of food also, and so lower rather than raise acidity. It is specially likely to do this when given too concentrated, or in too large a quantity at one time. (2) When absorbed it may be overpowered by alkaline salts of potash or soda present or produced from other sources (as debility, perspiration, etc.). It is always necessary, therefore, to see that an acid given raises the acidity of the urine. (3) There may be no uric acid in the blood owing to its previous removal by a course of salicylates or other solvents, and then there is obviously nothing for the acid to act on, and no gout results.

I notice that, Dr. Luff in his recent Goulstonian Lectures (*Lancet*, i. 1897, p. 1070) objects to my statement that diminished alkalinity of the blood causes retention of uric acid in certain tissues, and he then goes on to speak of the solubilities of sodium biurate. But why trouble about sodium biurate? I should acknowledge that the uric acid if long retained may eventually become sodium biurate, but we have to deal with it at the time it is in the blood, when according to Sir W. Roberts it is a quadriurate; for acids diminish and alkalies increase the excretion of uric acid in the urine from hour to hour almost from moment to moment, and the presence of more or less irritation in some fibrous tissue is a frequent concomitant of the diminished excretion in the urine; but here we are dealing with uric acid as it is in the blood and tissue fluids, and that it eventually becomes a biurate when deposited in the tissues is a matter of no consequence.

All the uric acid with which I am concerned in this book probably exists as a quadriurate, either in solution or in colloid form; and only in this and the next chapter have I to deal at all with the biurate of sodium, and that only *after* the arthritic irritation has been produced. For we often see the biurate plastered over joints

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and not causing an atom of irritation (see also my reference to Pfeiffer's experiments on himself in chapter xvi). When uric acid is being retained in the body by the action of an acid it is as a quadriurate, and probably in colloid form, but still in suspension and non-crystalline (see p. 154). And when it is being excreted in excess as the result of taking an alkali this again meets with it in the blood or tissues, probably as a quadriurate.

Now, Sir W. Roberts tells us, "Uric acid, gravel, and gout," p. 86, that the acid urate of sodium is not thrown down from a solution of quadriurate in serum till the second or third day, and it seems probable that in the living tissue fluids it will take even longer than this.

But Sir A. Garrod tells us in the passage already quoted above, that "a few glasses of wine, ale, or porter quickly—produce," etc., and we see in fig. 57 that the arthritic pains were very marked within an hour after swallowing the dose of acid, obviously then the arthritis could not be due to deposition of the biurate, but was probably due to retention of quadriurate either in solution or more probably in colloid form, and this is what I have been suggesting for years past in previous editions, not deposition, but *retention*.

And if this is correct we have here probably one rather important difference between the arthritis of gout and that of acute rheumatism.

In acute rheumatism the arthritis is often only a matter of a few hours, for even if it continues, the irritation may leave one joint and go to another, proving that the urate is soluble and can be moved from place to place.

And this is almost certainly due to the soluble quadriurate, and the biurate has not had time to be deposited: hence in acute rheumatism there is but a passing inflammation similar to that in gout of the fibrous tissues as described in chapters xvi. and xvii. and in fig. 65; and here the soluble quadriurate is all taken up again into the circulation, and leaves little or no deposit of acid urate behind it (see also chapter ix.).

In gout on the other hand, the urate is not only present in greater quantity in the one joint affected, but it remains longer, and so the biurate is deposited, and this may go on for some time as long as the blood is rich in urates attracting other urates to it, so that the tophus grows steadily larger and larger.

Here we have undoubtedly to deal with the biurate, and have to consider its solubility in any attempt we may make to dissolve and remove it.

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But here again the chemical facts are not nearly so difficult to reconcile with clinical experiences as some appear to believe.

Thus Sir W. Roberts tells us that the biurate is not entirely insoluble in blood serum, and again he says (prev. ref., p. 108), "The solvent relation of the bodily fluids to the material of gouty deposits is simply a question of saturation or subsaturation. If the lymph or synovia at a certain spot became saturated or rather supersaturated with sodium biurate, precipitation of that substance will inevitably take place into the contiguous fibrous tissues. And if after such an event the lymyh or synovia recover their purity and become approximately free from biurate, as in due course usually comes about, a process of slow resolution will of necessity set in."

Now this is very interesting, and it explains a clinical experience of mine that one often appears to get more benefit as regards the clearing up of old gouty troubles from several short courses of salicylates with pauses between them than from a single long course, and each time one starts fresh, one gets a large excretion of uric acid, though towards the end of the previous course it had been but little increased.

And the results given in my curves show that the effect of leaving off salicylates after some days' administration, is a great fall in the excretion of uric acid in the urine, which is thus for some days considerably below its normal relation to urea, and it seems probable that during these days the lymph is in a condition of subsaturation and some resolution of biurate deposits consequently occurs.

Again, and this is a matter of the greatest interest Sir W. Roberts shows (prev. ref., pp. 79 and 80) in his experiments, that the biurate is comparatively soluble in water, and that the solvent power of serum or a saline solution increases as the percentage of saline it contains diminishes.

And it follows from this that a blood which is watery and poor in salines, is a much better solvent of biurate deposits than a blood which is concentrated and rich in salines.

And this is exactly what we find in nature, for as I have been pointing out over and over again in the previous chapters (see p. 196 and elsewhere), it is in the old feeble debilitated and water logged, that we get a constant excess of uric acid in the urine, and what appears to be a comparatively rapid removal of biurate deposits from gouty joints, soon leaving little but erosion to mark the place where they were.

Now, as we have seen in previous chapters, the mere presence of

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an excess of uric acid in the blood makes it dilute and watery by diminishing the outflow of water from the kidneys, so that we get in chlorosis, as Dr. Jones has pointed out (see chapter xii., p. 415), not only a lowering of the blood decimal but a fall in the specific gravity of the blood.

And the same in Bright's disease, when there is retention of water and dropsy, the blood (as in the case examined in chapter xiii., p. 466, for instance) is poor and watery, and contains but a low percentage both of hæmoglobin and cells.

And this is not all, for in conditions of weakness, debility and emaciation, we get low nutrition and slackening of digestion and metabolism in general, and as a result of these, very low excretion of urea per pound of body weight.

But the urea is the index of the breaking up of albumens and albuminous tissues, and while the nitrogenous portion of these go to produce this urea, their salts no doubt furnish the corresponding saline constituents of the blood and urine, and hence, as I have shown, the acidity of the urine varies up and down with the urea.

Therefore, in conditions of debility, wasting, and especially if there is dropsy, we have two very powerful conditions tending to make the blood and its serum watery and poor in salines, and this will, as we have seen, directly increase their power of dissolving biurate deposits.

Again, it is not to the point with regard to the large excretion of uric acid in the urine produced by the administration of alkalies, or the diminished excretion produced by acids and acid salts, etc., to show that the solubility of the biurate is not increased by alkalies: for in all physiological conditions, and probably in all pathological ones also, with the exception of gout and rheumatism of some standing, we have to deal only with uric acid, or a quadriurate of which the solubilities are as we know very different from those of the biurate, and which do comparatively, easily pass into solution in combination with an alkaline base, and are also precipitated from such solution by an acid which takes the base from them.

In so far as alkalies and their administration affect the solution and removal of biurates from the tissues, their first effect is no doubt to remove uric acid or quadriurates and eliminate them from the body, and if this, as in the case of the salicylates above mentioned, causes subsaturation of the blood and tissue fluids, then some biurate is taken up from the deposits.

Hence the elimination of gouty deposits by the administration

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of alkalies is probably, as Sir W. Roberts points out (prev. ref., p. 129), a somewhat slow process: though in taking his estimate of their effects we must make allowance for the constant daily introduction of uric acid or xanthins in food, which was probably, in the cases he is speaking of, neither prevented nor allowed for.

Again, also, it is little to the point to show that salicylates have but small effect on the solubility of the biurate, for both in physiology and pathology, when they cause a plus excretion of uric acid, they have to deal probably entirely with the quadriurate; and if chemistry is correct they apparently have the power in conditions obtaining in the living human body of splitting this up into its constitutents, and combining with only one of them, the glycocoll; and this power has, as I have pointed out in chapters ii. and iii., some relation to the salines in the blood and the acidity of the urine, in relation to urea; and cannot therefore apparently be exercised in dogs.

Other things which interfere with the solubility of uric acid (such as iron, lead, mercury, lithia, zinc, manganese, calcium, etc.) may also produce an attack of gout, but compared to acids they are rarely met with in nature, and are not generally so powerful in action, as a good supply of alkaline phosphates or other alkaline salts easily prevents their producing much retention. Still at night, when the acidity is high, they produce a little or increase any pain that is present.

Of iron salts, Sir A. Garrod says (p. 383): "These preparations, when indiscriminately given to gouty subjects, are apt to excite paroxsyms of their disorder, and are, for the most part, contra-indicated."

That lead precipitates gout attacks is so well known that I need hardly quote anything concerning it, but Sir A. Garrod has shown that gout is much more common among those exposed to lead, such as plumbers and painters. He also pointed out that uric acid is almost invariably present in the blood in cases of lead poisoning.

I would remark, in passing, that it is during the secondary action of lead that there is collæmia. Its primary action is, as I have shown, to diminish the solubility of uric acid, to bring excretion below formation, and to retain it in the body, and at this time there is little or none in the blood. Then, when from dyspepsia or intestinal pain (due to urate of lead in the intestinal walls, see pp. 335 and 340), the urea and acidity fall, the retained uric acid is washed out into the blood stream, and collæmia with

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slow high tension pulse accompany and follow the lead colic. If my researches are correct, the slow high tension pulse which is often very marked in plumbism may be taken as proof positive of the presence of excess of uric acid in the blood, and the pulse can be quickened and its tension reduced by drugs that act on uric acid, and they may produce gout when so acting. Again, I have in my own case often produced (as it is easy to do) both the primary and secondary action of lead.

As to mercury, I have shown that its administration brings the excretion of uric acid below the level of formation (*British Medical Journal*, 1890, vol. i., p. 1,241, also fig. 17, p. 60), and clears the blood of it, producing mental well-being, free capillaries, and quick low tension pulse and diuresis, all results of the free capillaries.

It also resembles lead in that it produces in my own person at least some intestinal pain of a griping character.

Sir A. Garrod says of it (p. 236): "It is a well-established fact that metallic impregnation is capable of inducing pains in the extremities, which bear a close resemblance to those of rheumatism." Artificers exposed to mercurial vapour often suffer from what is termed "neuralgia mercurialis."

With regard to lithia, I must refer to what I have said of its action on p. 51. My results show that it diminishes the excretion of uric acid, and at the same time frees the capillaries and quickens the pulse, causes mental well-being and a free flow of urine, and when it does all this it generally causes, like lead and mercury, some pricking and shooting pain in the joints also.

Now the mineral waters containing sulphates spoken of in the previous chapter as curing glycosuria and diabetes, and as doing this by clearing the blood of uric acid, are many of them, strange as it may seem, useful in the treatment of gout also.

Now, they cure the diabetes by clearing the blood of uric acid and allowing combustion to improve, and we should expect that in doing this they would produce more or less arthritis, and this is exactly what we find to be the case; still, nevertheless, they do good for gout, because once this first arthritis has passed over they tend to keep the blood free from excess of uric acid for some time, and in this way keep off attacks.

This is the way in which a large number of drugs, as iodides, salts of calcium, cannabis indica, lithia, guaiacum and other resins, and compounds of sulphur, such as the troch. sulph. Co. of Sir A. Garrod, act in relieving chronic arthritis associated with debility, and almost completely free from febrile temperature.

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These troubles are due to the fact that there is chronic uric-acidæmia, and every little rise of acidity, such as that which occurs every night, tends to drive almost every evening a little more urate into the joints, and keep the irritation smouldering on, but if any of the above-mentioned drugs can keep the blood relatively free from uric acid, much of this chronic irritation may be prevented; but these drugs also when first used may make the pains worse for a day or two.

This is exactly the condition (chronic arthritis associated with debility) in which salicylates will do no good, and may even, as we shall see in the next chapter, do harm.

Exactly the same thing holds with regard to the mineral waters which contain sulphates; the patients arrive at the spa with a considerable quantity of uric acid in their blood, and the sulphates drive this into their joints and produce an arthritis, and I believe that at several such spas the physicians are in the habit of telling their patients that this first attack is a sign that the water is going to do good.

And this is quite true, for once the first attack is over the sulphates keep the blood relatively clear of uric acid, and thus prevent future attacks for some time.

And they produce these results (1) by clearing the blood of uric acid; and (2) by the increase of metabolism and combustion which results from this, and which, as we have seen, cures the diabetes, and the result of this upward metabolism is that the fires of life in this patient burn for a considerable time both brighter and better, acidity of urine remains high, and alkalinity of blood low, and the blood is kept relatively clear of uric acid for some months, so that there is no arthritis.

But let the patient leave off the drug or the mineral water, and when after a few months his combustion has come down again he will again have uricacidæmia, and each rise of acidity will then increase the irritation of his joints.

In this way the cure of the arthritis is not permanent, but has to be repeated from year to year; indeed, there is obviously no cure for these diseases but such alterations of diet as limit the introduction and formation of uric acid, and, at the same time, provide for its steady and continual elimination, thus gradually removing the quantities previously stored in the body.

Speaking generally, it may be said that all the diseases in the preceding fourteen chapters may be cured by such a drug as the iodide of mercury, which clears the blood of uric acid, but that this

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drug, or any other acting like it and removing the uricacidæmia, may, in doing so, very probably produce arthritis (as we shall see in the cases recorded in the next chapter), but if it does not produce arthritis at once, then its continued administration will keep the blood clear of uric acid, and, for a time, prevent arthritis; such drugs can, in fact, produce arthritis only when they find a lot of uric acid in the blood. On the other hand, it is nearly always possible to produce an arthritis by giving a solvent of uric acid, such as an alkali; thus, if some bicarbonate of soda is taken in the afternoon, this brings a little extra uric acid into the blood, and when the ordinary evening rise of urinary acidity (or fall of blood alkalinity) supervenes upon this, there is pricking and shooting in the joints; but this would not have occurred if the alkali had not been taken, because there would have been less uric acid in the blood—so little, in fact, that the rise of acidity would have produced no noticeable effect on the joints; and we have here as it were a summary of the whole action of uric acid in the causation of disease.

In the same way a purely nitrogenous, or highly animal diet, may, like the drugs and mineral waters mentioned above, not make an arthritis worse, but better; for meat, and even uric acid itself, are stimulants to nutrition, because they clear the blood of uric acid and start an upward metabolism, and so long as the fires of life burn brightly the blood is kept clear of uric acid, and there is relative freedom from arthritis.

But a time comes in every case when this stimulation is no longer possible, when the fires of life, from age, over-work, and other causes of exhaustion, burn so low that they will not re-act to any stimulus, and then neither meat nor uric acid will do any more good; and then, instead of acting as stimulants the uric acid gets at once into the blood, and causes the most terrible depression of mind and metabolism.

So long as stimulation continues the patient is very pleased with the result, his arthritis is better, and he is better and stronger in himself; but he cannot leave off his stimulants, they have, on the contrary, to be steadily increased, or all his troubles tend to return, and at the end, which is sure to come, he will have the most disastrous uricacidæmia without any chance of escape from its fatal results.

I believe therefore that the treatment of chronic arthritis by a pure meat diet is a most dangerous treatment, though in some cases, and where it acts as a stimulant, it may, for a time, relieve the

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arthritis: but where it fails to act as a stimulant, or after the stimulation passes off, it may produce most serious results, and even in the last two years I have seen it apparently produce severe depression, headache, sleeplessness, and anæmia (all the signs in fact of collæmia) and in one case even fits ending in prolonged coma. Then I notice that Dr. Armstrong of Brixton, who recently read a paper at the Medical Society on this treatment in chronic gout (see *British Medical Journal*, May 1 and 15, 1897) gives as one of his conclusions in the original paper that patients "recover equally well whether on this (pure meat) dietary or on the meat-free dietary suggested by Dr. Alex. Haig"; if this is so, there is no shadow of doubt in my mind as to which diet is the safer of the two, and after the above experiences no one for whom I am responsible shall ever be put on a pure meat diet.

In pathology we see that a gout attack is brought on by indulgence in wines and beers, which are more or less strongly acid. Champagne is about the most acid of wines, and the cheaper beers are generally more acid than those of better quality. I found acidity equivalent to 18 grs. of oxalic acid in a pint of 4d. ale, and 25 grs. in a pint of stout. Sherry 37 grs. in a pint. Port about the same. Claret 46 grs. to the pint, and champagne 49 grs. to the pint.

Sir A. Garrod says (p. 226): "As regards acidity, Dr. Bence Jones has ascertained that wines may be arranged in the following order, beginning with the least acid:—Sherry, Port, Champagne, Claret, Madeira, Burgundy, Rhine wines, and Moselle. All the wines are found to be more acid than malt liquors," but as the quantity of malt liquor taken is generally much greater than that of wine, the total amount of acid taken in may be greater in those who drink beer than in those who take wine.

Then the late Dr. G. Harley has pointed out the interesting fact (*Lancet*, 1896, vol. ii., p. 309) that the Champagne used in England is often more acid than that used in other countries.

A good class cider has an acidity equal to 58 grs. of oxalic acid to the pint, but it also contains a lot of soda and potash, and the effect of taking it as regards the acidity of the twenty-four hours' urine is almost *nil*; I suppose, therefore, that its acidity is due to acid salts of vegetable acids which in the body are converted into carbonates, and as the acids and alkalies in cider or apple juice are nearly balanced there is no effect on the acidity of the urine.

With wines and beers, however, this is not the case, for either by formation of acids during fermentation, or by loss of alkali during

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fermentation, and keeping in the case of wine (tartar) the alkalies no longer balance the acids, and those beverages have a much more decided effect in raising the acidity of the urine than cider has; beer also is made from barley, in which acids preponderate over alkalies.

Fruits, again, are acid, owing to the acid salts they contain, but these become carbonates in the body, and act as doses of alkali rather than of acid, and they tend to lower the acidity of the twenty-four hours' urine.

I conclude, therefore, that while many wines and beers have quite a distinct effect in raising the acidity of the urine, and will consequently cause retention of urates in the body, and help to pave the way for gout, good cider made from pure fruit, unsophisticated, and apart from impurities such as lead, will do but little harm, and will tend to lower the acidity of the urine rather than to raise it, so that it may even do good and prevent gout.

In reference to this point about cider, I have been told by my friend Dr. Bonus, that a great friend of his, a native of Normandy, used to tell him that gout, gravel, and rheumatism were rare forms of disease there, and that this was attributed to the use of cider in place of wine: I believe that the same has sometimes been said of the cider drinking counties of England, and I have known one or two people who asserted that their gout or rheumatism had left them on their giving up wine and taking to cider.

Many fruits having a distinctly acid reaction tend to raise the acidity of the urine and diminish the alkalinity of the blood for an hour or two after they have been taken, and while they do this they often cause mental exaltation and well-being, with, perhaps, some pricking and shooting pains in the joints, or in a very gouty person, an attack may be precipitated; but at the end of this time their alkaline bases come into action, and there is a fall in the acidity of the urine and a rise in the alkalinity of the blood, which more than compensates for the previous fluctuations in the opposite directions, so that the effect of such fruits on the reaction of the urine of the twenty-four hours is to produce very little change or a slight fall of acidity.

Fruits, therefore, may be freely eaten by those who have not much urate in their blood, and they will not tend to cause a retention or accumulation of uric acid in the body, but rather the reverse.

I must confess that I find it difficult to understand the logic of those who, wishing to know the effects of wines on the human body,

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have satisfied themselves by looking up the percentage composition of such wines in a work on chemistry, and then finding that their order of acidity did not correspond with their apparent order of gout production, have thence concluded that their acids or acid salts had no effect on the human body, and nothing whatever to do with the production of gout.

Surely if the object is really to find out the effect of wines on the reaction of the fluids of the human body, it might be almost worth while to pour a known quantity of one or two of them into a human body, and watch their effects on the reaction of the urine for instance; and this is an experiment which can be begun and completed in three to four hours of any single day.

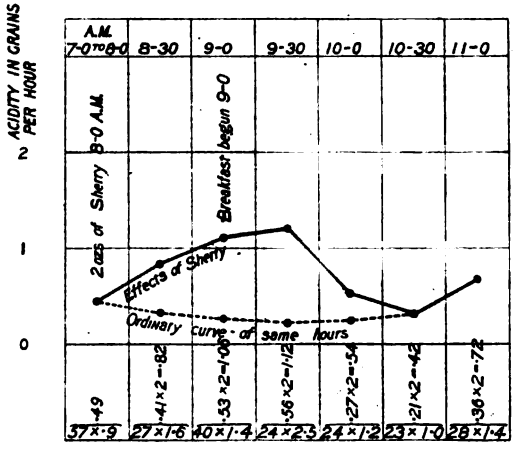

FIG. 54.—CURVE OF URINARY ACIDITY SHOWING THE EFFECTS OF 2-OZS. OF SHERRY.

The above view that the acids of wine are not the cause of gout because their acidity does not correspond with their recorded production of gout, appears to me also to quite lose sight of the obvious fact that the effect on the body depends not only on the acidity of the wine but also on the quantity taken, so that beers of comparatively low acidity taken by the pint may nevertheless produce as much or more effect than the more acid wines only taken by the ounce.

Now fig. 54 shows the effect on the acidity of the urine of taking 2 oz. of sherry at 8 a.m.

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The first point on the curve is the excretion of acid for the hour ending 8 a.m., the other points are the excretions of half-hours multiplied by two to make them comparable to the first point. The figures below are the hourly and half-hourly excretions of urine in cc. multiplied by the number of cc. of standard soda solution required to neutralise them.

The lower broken curve is that of a control day for comparison.

No food was taken for an hour after the sherry, by which time it had caused a very distinct rise in the acidity of the urine, a rise which is never seen in the normal curves of these hours (see fig. 3).

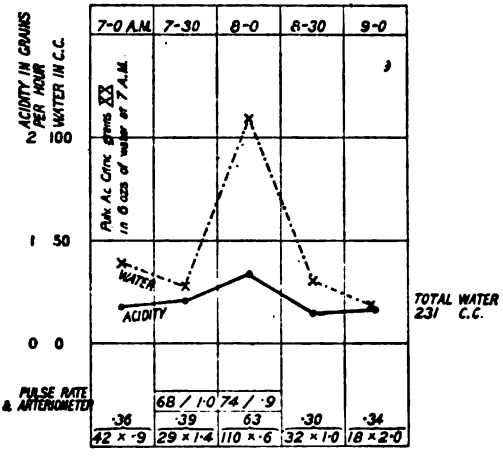

FIG. 55.—CURVE OF URINARY ACIDITY AND WATER SHOWING THE EFFECTS OF 20 GRAINS OF CITRIC ACID.

Note also that with the rising acidity the urinary water rose to 40 cc. in the half hour ending 9 a.m., that it fell to 24 cc. at 9.30 and 10 is the generally constant result of the commencement of digestion; fluid being then required for gastric juice: the rise of acidity at 11 common to both curves is also a constant result of the later digestion of breakfast.

It seems clear then that these 2 oz. of sherry produced a very distinct effect on the acidity of the urine.

Fig. 55 shows a somewhat similar result from taking gr. xx. of citric acid in 6 oz. water at 7 a.m. The upper curve is that of water in cc. per half hour, and the lower that of acidity of urine in

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grains per half hour, and as they are all for periods of half an hour none of them are multiplied by two.

The taking of the acid is followed by a rise of acidity to ·39 at 7.30, and to ·63 at 8, and a fall to ·3 at 8.30, when the ordinary curve appears to be resumed.

And now again note the urinary water (upper curve). It fell to 29 cc. in the first half hour, but rose to the great height of 110 cc. in the second half hour after the acid, and corresponding to the greatest rise in the acidity curve.

Note also the effects on the pulse rate, and tension in the figures under 7.30 and 8 a.m. These read from left to right. 7.30 a.m., pulse rate 68, position sitting, diameter of left radial by arteriometer 1·0 millimetre; and under 8 a.m., pulse rate 74, sitting, left radial diameter ·9 of a millimetre.

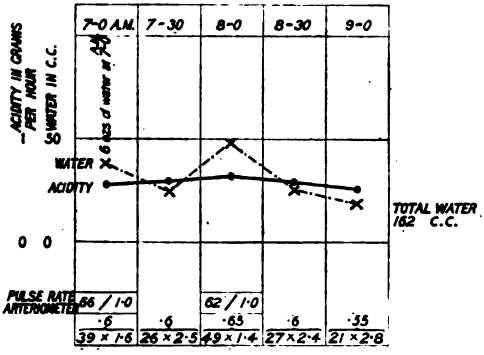

FIG. 56.—CURVE OF URINARY ACIDITY AND WATER CONTROL TO FIG. 55.

We see then that along with the rise of acidity at 8 a.m. there was a quickening of the pulse, a fall of blood pressure, and a marked diuresis; and these last were all results of one and the same cause, the relative clearing of the blood of uric acid which the rise of acidity or fall in the blood's alkalinity produced.

We see also that the total urinary water in the two and a half hours ending 9 a.m. was 231 cc.

And now look at fig. 56, which is a control on another morning, when 6 oz. of pure water were taken at 7 a.m.

We see here that the acidity curve is nearly a straight line, that the water also fluctuates but little, its highest point being at 8 a.m., which is also the highest point of acidity; but there is no diuresis

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corresponding with that in fig. 55, though the same quantity of water was taken at the corresponding hour, and we see also why there was not, for the pulse remained slow and was indeed slower at 8 than at 7, and there was no reduction in the diameter of the radial artery.

And we know why this was so, for there was no appreciable rise of acidity and no clearing of the blood from uric acid, and consequently the capillaries of the kidneys remained obstructed and the blood pressure did not fall.

Hence we see that the total water in the two and a half hours ending 9 a.m. on this day was only 162 cc. as against 231 in fig. 55, thus again proving what I have been saying for years, that the uric acid controls the excretion of water, and not the water the excretion of uric acid.

It is true that the water in the half hour ending 7 a.m. was 39 cc. in fig. 56 and 42 cc. in fig. 55, but that in the half hour ending 8 a.m. was only 49 cc. in fig. 56 against 110 cc. in fig. 55, and this accounted for most of the excess of the one total over the other, and it was clearly due to a freeing of the capillary circulation in the kidneys.

That the acidity curve as a whole is higher in fig. 56 than in fig. 55 is merely due to the fact that urea was higher on the one day than the other, as acidity rises and falls with urea when other things are equal.

I think these figures show pretty clearly not only the effects of citric acid on the acidity of the urine and the alkalinity of the blood, but also demonstrate once more what I have long known, namely, that I can alter at pleasure the rate of the heart's action and the diameter of the radial artery that is the blood pressure, and can free from obstruction the capillary circulation not of the kidneys only, but also of the lungs, liver, muscles, skin, and indeed of the whole body: but that I have absolutely no power to do this at all except by altering the quantity of uric acid in the blood of which the quantity passing in the urine is the index; and this again explains the fact which is practically constant in physiology that the excretion of uric acid and of water in the urine move from hour to hour and day to day in opposite directions, and everything that alters the uric acid may be depended upon to alter also the water.

I did not estimate the uric acid in fig. 55 at 8 a.m., but I am as certain that it fell then, as I am sure that I should have found increased excretion of water from the lungs as well as from the kidneys if I had looked for it.

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It is not everyone who can give the time required to estimate the acidity of the urine or the diameter of the radial artery, still less the excretion of water from the lungs from half hour to half hour, but everyone can measure the urine from half hour to half hour and note the alterations in the pulse rate, and these would often give quite sufficient indication of the action of the drugs taken on uric acid; and when the doses taken and effects produced were somewhat larger than in these figures, quite distinct effects on the blood decimal could no doubt also be produced (see figs. 46 and 65).

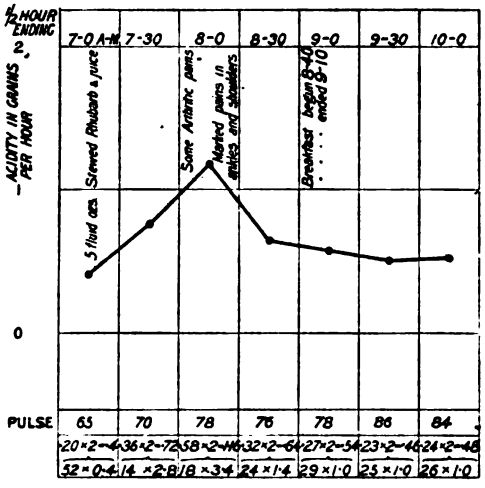

FIG. 57.—CURVE OF URINARY ACIDITY SHOWING THE EFFECTS OF STEWED RHUBARB.

They must not expect, however, to produce results like those shown in these figures, except under the conditions which obtained in these experiments: that is, they must attempt to raise the acidity at a time such as the morning hours, when it is naturally steady or falling, and those again whose hourly excretion of acid is from differences in diet, etc., much greater than mine, must not expect to produce results comparable to mine except by using larger doses of acids.

Fig. 57 shows the similar results of taking 5 fl. oz. of stewed rhubarb and juice at 7 a.m.

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Here again we see a marked and decided rise in the acidity of the urine in the first hour after taking the dose, followed by an almost equally marked fall in the third half hour after it.

Here the pulse rate was counted, but no measurements of the radial artery were made, and we see that the pulse quickened from 65 up to 78 with the rising acidity, and fell to 76 as the acidity fell: that it rose again to 78, 86 and 84 at 9, 9.30 and 10, merely shows that the digestion of breakfast was then going on.

But part of the quickening of the pulse at 7.30 and 8 a.m. was no doubt due to the digestion of the rhubarb then going on in the stomach, and we see the same thing from the urinary water, which instead of rising with the rise of urinary acidity at 7.30 and 8, as in fig. 55, fell from 52 cc. at 7 a.m. to 14 and 18 cc., rose to 24 and 29 cc. at 8.30 and 9, and again fell to 25 and 26 cc. at 9.30 and 10, owing to the demand for water in the digestion of breakfast.

In fig. 55 there was practically nothing for the stomach to digest, and so the water was free to rise when the rising acidity cleared up the collæmia and freed the capillaries of the kidney. In fig. 57 these capillaries were no doubt also free at 8 a.m., but the blood was then poor in water owing to the pouring out of digestive fluids, and there was no diuresis.

And this effect of digestion must always be kept in mind in estimating the effect of drugs on collæmia and the renal capillaries as shown by diuresis.

The very marked arthritic pains about 8 a.m. (fig. 57) in the ankles and shoulders showed where the uric acid had gone to, and no doubt if there had been any available water there would have been a diuresis.

A large number of fruits containing acids or acid salts produce similar rises in the acidity of the urine for an hour or two after they are taken, with similar quickening of pulse rate, and a relative diuresis, with mental brightness and well being, and more or less arthritic pain: but very few of these in the quantities commonly taken suffice to produce any visible effect on the acidity of the twenty-four hours, the effect is no doubt there but it is so slight as to be only with difficulty distinguished from that due to other causes.

It is clear, then, that acid wines and acid fruits do affect the acidity of the urine, the alkalinity of the blood, and the solubility of uric acid.

In the case of fruits this effect is temporary and transient, for

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later on their alkaline bases come into action, and reverse the above effects; but in wines the alkali has either been removed from the grape juice or fresh acids have been formed or added; and beer has, for other though similar reasons, an excess of acid.

Before leaving the acidity of wines, however, we have to consider the effects of one of their other constituents, namely alcohol.

Now Professor Vaughan Harley has pointed out that alcohol increases the excretion of uric acid, and it is scarcely likely that it does this in any way except, like very numerous other substances mentioned in this book, by affecting its solubility.

I have therefore taken alcohol in various forms, with a view of testing this effect, and my results seem to show that it more or less

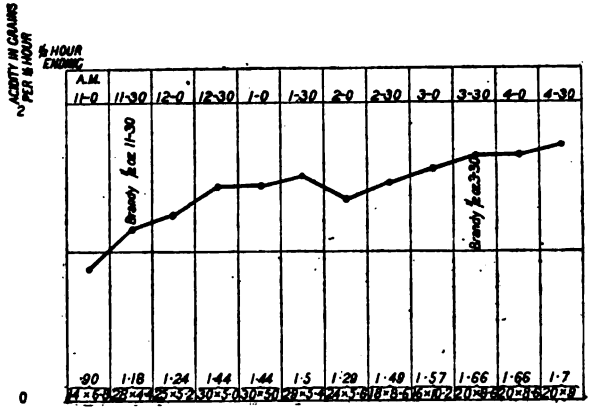

FIG. 58.—CURVE OF URINARY ACIDITY SHOWING THE EFFECT OF TAKING BRANDY UNDILUTED.

distinctly diminishes the acidity of the urine, and like other things which do this, increases for a time the excretion of uric acid.

In fig. 58 I show the effect of two small doses of brandy, the first at 11.30 a.m. and the second at 3.30 p.m., and in both cases its ingestion appeared to be followed by a distinct break in the upward curve of acidity. In the half hour ending 11.30 before the brandy, the acidity rose from ·90 to 1·18 or ·28, but in the half hour ending 12 noon it only rose to 1·24 or ·06, and in the half hour ending 12.30 it rose again more quickly to 1·44 or a rise of ·20, and it seems therefore evident that the effect of the ½ oz. of brandy was to diminish the rise in the half hour ending 12 noon, just after it was taken.

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Similarly in the half hour ending 3.30 p.m. the acidity rose from 1·57 to 1·66 or ·09, but in the half hour ending 4 p.m., after the brandy was taken, it did not rise at all; but it does rise again slightly in the half hour ending 4.30, making it probable that it would have risen at 4 p.m. also but for the brandy.

If the curve had risen steadily from 11.30 to 12.30 it should have stood at 1·31 at 12 noon, but it only reached 1·24, a loss of ·07; similarly the dose of brandy at 3.30 appeared to do away with a probable rise of about ·09.

I have several curves showing what appear to be very similar results from taking small doses of alcohol without water, and if we may look upon them as results we shall not have much difficulty in understanding how they are produced.

For alcohol and spirits generally act as irritants of mucous membranes whether of mouth, throat or stomach, and this is especially the case when they are taken alone without any added water.

Now if brandy thus irritates the mucous membrane of the stomach it may stop for a few moments the processes of digestion and absorption there going on.

But as we already know the rise of acidity from 11 a.m. onwards is almost certainly due to the digestion of breakfast and the absorption from the stomach of acids and other products of digestion; just as the rise from 2 onwards is due to the similar digestion of lunch, therefore anything that interferes with digestion will interfere with the rise of acidity.

And we have tolerably clear evidence that alcohol does interfere with gastric digestion in the well-known fact that in those not accustomed to it, or in those who take it in unusually large doses, it may cause nausea and complete loss of the contents of the stomach at once by vomiting, or it may merely suspend digestion, the contents of the stomach being vomited more or less unchanged several hours later.

I think, therefore, that in the case of some wines rich in alcohol their effect on acidity would really be somewhat greater than that shown in the case of sherry (fig. 54), but for the alcohol they contain and its irritant action on the gastric mucous membrane.

It may also be interesting to remember here, as I have already pointed out in chapter ii., that the mineral acids, if given in too large quantity, or insufficiently diluted, irritate and cause pain in the stomach, and then cause a fall in the acidity of the urine in place of a rise.

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Sir A. Garrod says (p. 212): "That women are less subject to gout than men is beyond doubt." He attributes this to difference in character and habits, and adds "besides which a most powerful counteracting influence exists in the presence of the catamenia during a considerable portion of their lives."

As to habits, women are generally less exposed to weather (cold and wet), and take less of beers and wines than men, and as to the catamenia I have shown (fig. 30) that menstruation lowers acidity and produces uricacidæmia and a plus excretion of uric acid, and this occurring for four or five days in every month may sensibly diminish the amount of uric acid that is stored in the body.

As to the effect of age I mentioned some points at the beginning of the chapter, and shall speak of it again in the chapter on rheumatism.

In estimating the effects of beers, wines, and other beverages on different races, it is necessary to bear in mind the amount of meat or nitrogenous food they consume, as this determines the introduction as well as the formation of uric acid, and obviously an acid will produce most effect and most quickly store sufficient uric acid to cause gout where it has most to work upon, and the formation and introduction are greatest. Thus in England beers produce more gout than in Germany, because the English consume more meat per head of population than any other nation in Europe (see *Lancet*, 1890, vol. ii., pp. 409, 468, and 589).

Speaking of nationality reminds me of the fact that the Scotch suffer from gout comparatively little, so that our brethren north of the Tweed have difficulty in finding cases on which to work. I have no doubt that this is due to the fact that the national beverage of the Scotch, namely, whiskey, contains little or no acid, and affects acidity but little, and the Scotch also, as a rule, eat considerably less animal food than the English. If a Scotchman comes to England and drinks beer and wine and eats meat, he suffers from gout like the Englishman. Sir A. Garrod says: "The least acid of all alcoholic fluids are geneva and whisky."

(For similar facts about the incidence of gout in Persia see chapter xvii.)

It is generally agreed that excess of animal food is a cause of gout, and Sir A. Garrod quotes several authors to this effect, and he also says, on p. 230, "Cullen remarked that gout seldom attacked persons employed in constant bodily labour, or those who live much upon vegetable diet."

Figs. 39 and 40 demonstrate what would probably be the effects

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of constant bodily labour, and the evil effects of a highly animal diet are evidenced by the figs. from 24 to 28.

Dyspepsia may have an important influence, as I mentioned in speaking of Sir A. Garrod's quotations from Sydenham. It seems probable also, as pointed out by Bouchard, that acids may be formed under certain conditions or out of certain articles of food, and these would, no doubt, affect the solubility and excretion of uric acid, so long as they continued to be formed.

It has been assumed by several writers, notably by Murchison, that in certain conditions of functional disturbance of the liver there is an excessive formation of uric acid. If they mean that uric acid is formed in greater proportion to urea than 1—35, I can see no good evidence of it, and I look upon the excess of urates in the blood and urine as the sign of excessive excretion, the result of previous minus excretion or retention, and dependent upon increased alkalinity of the blood. If they mean that in certain liver troubles, especially those accompanied by slight fever, there is excessive formation of both uric acid and urea, in their normal relation to each other I should raise no objection.

Among the symptoms of the dyspepsia connected with the uric acid diathesis mentioned by Sir A. Garrod (previous reference, p. 232) are many which I have attributed to collæmia, as "oppression and frequently sleepiness after food." "Saliva and buccal secretion often more adhesive than natural." I have pointed out that saliva is scanty in the collæmia of the opium rebound, and at the time of the uric acid headache, mental depression, &c., in all cases no doubt due to the same cause, namely, obstruction of capillaries by uric acid. "Accompanying these symptoms there is a scanty secretion of urine which is highly coloured and strongly acid." I have pointed out that the urine is scanty in the collæmia of the uric acid headache and mental depression, and that the water in fact varies inversely as the uric acid excreted along with it, and the water is scanty probably for the same reason that the saliva is scanty because the vessels of the kidney are obstructed.

As to high acidity, that is only relative to the water. If the urine of 24 hours is saved it will be found that the total acidity is really considerably lower than that of the previous day, when there was less uric acid and more water, unless, as I have before explained, there is a very great excess of uric acid in the urine, such as is met with in severe headache, epilepsy, paroxysmal hæmoglobinuria, and similar conditions, and then the quantity of uric acid present may be sufficient to raise the acidity of the urine very decidedly.

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Much sedentary work tends to produce gout. Sir A. Garrod quotes (p. 233) Sydenham, as saying, "Whenever I returned to my studies gout returned to me," and I have already given his quotation from Cullen about the preventive power of bodily labour.

I have pointed out that the excretion of uric acid is greater in summer than in winter, and Sydenham speaks of gout as a winter disease. Now, there is no doubt that a labouring man has, so to speak, summer all the year round. His exertions keep his skin constantly active. He gets rid of a large amount of acid in this way, hence the acidity of his urine rules low, and the alkalinity of his blood is well maintained; he therefore excretes uric acid freely, and retains but little in his body, and so, as observed by Cullen (previous quotation), he but rarely suffers from gout, and this is so almost without regard to his diet, for he excretes all the uric acid he introduces, as well as all that he forms. As to the acidity of the sweat, see also Heuss, *Monatsch. fur Prakt. Dermatol.*, Band xiv., Nos. 9, 10, and 12, and *Lancet*, 1892, vol. ii., p. 1,118. A sedentary man has not only higher acidity and retention of uric acid, but his circulation, especially in peripheral parts like the hands and feet, is less well maintained, and as a result the alkalinity of the fibrous tissues in such parts is also less well maintained.

Though, as I have said, I used to have headaches when my life was not sedentary, I have no doubt that I could indulge in meat and beer with comparative impunity if I lived the life of a labourer.

After what I have said about the effects of summer, it is not surprising to find Sir A. Garrod saying (p. 235), "Gout is undoubtedly much less prevalent in hot than in temperate climates," though, no doubt, as he remarks further on, food and habits have also something to do with its absence.

The reverse effects of cold need hardly be gone into, but Sir A. Garrod says (p. 247): "When cold acts as an exciting cause the effect is due, at least in part, to its arresting the secretion of the skin, and checking the escape of acid from the surface," and my experimental experience is in complete accord with this statement.

I notice with interest that Dr. Solly says (prev. ref., p. 179), "The geographical distribution of gout is chiefly due to diet, drinking, and the social habits of the residents in countries where it is most prevalent, as in England, for example"—a statement which I can most cordially agree with, for gout owes, not only its geographical distribution, but its entire existence, to diet.

Local injury will, no doubt, diminish the alkalinity of the affected part, just as fever diminishes the alkalinity of the whole body, and

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Sir A. Garrod says, "Local injury not only acts in exciting gout, but frequently determines the situation in which the inflammation will show itself. Thus, injury to the knee or ankle will usually cause these joints to be primarily affected, although the great toe or some other part, may subsequently become implicated."

We shall see presently that in rheumatism local injury has the same effect, and compare the above quotation with what I have said as to the effects of exercise in determining the seat of the gouty arthritis.

Hæmorrhage is recorded by Sir A. Garrod as an exciting cause, and he attributes its effect to the "nervous depression" it produces. It seems to me, however, that another explanation is possible. First of all the blood is alkaline, and loss of blood is practically equivalent to removal of alkali from the body. Then it is well known that when the temperature is normal, severe loss of blood from any cause will raise it, and fever, as we have seen, raises the acidity. We have, therefore, two results of severe hæmorrhage, which, acting together, diminish the alkalinity of the blood and tissue fluids. This interferes with the solubility of uric acid, and tends to precipitate it upon certain of the least alkaline tissues, namely, the fibrous tissues in the joints and elsewhere.

With regard to the raising of the acidity by fever, I am not quite sure that it should not be put the other way, and that it might not be more correct to say that rise of acidity or fall in the alkalinity of the blood causes fever. We have seen that acids stimulate nutrition, metabolism, and combustion throughout the body, and cause a rise of urea and a rise of temperature if they produce a fall of uric acid, and if microbes and other materies morbi reduce the alkalinity of the blood they must of necessity cause an increase of metabolism and combustion, and this, as I have suggested, may be nature's reaction, and an attempt on her part to burn up the invading microbe, in which endeavour we should, in my opinion, be ready to give her all the help in our power (see p. 319).

It is not a little interesting to find that acids stimulate both animal and vegetable nutrition, as, I believe, it has been shown that the growth of seeds and young plants can be very greatly stimulated by watering them with very dilute acids.

In any case the difference between the increased combustion we can produce with such drugs as the iodide of mercury, which quickens the pulse, raises the temperature, increases urea and diminishes albumen or sugar, and that of fever, cannot be more than one of degree,

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and I have also shown that in physiological conditions the quantity of uric acid in the blood really controls to a very considerable extent the formation and distribution of body heat (see fig. 5 and also chapter viii.).

That, as Sir A. Garrod relates, sudden stoppage of menstruation should produce gout, is not very extraordinary, for menstruation is commonly accompanied by uricacidæmia and its signs (figs. 30 and 31), and any exposure to cold or febrile disturbance supervening upon this would, undoubtedly, drive the urate out of the blood into the joints, and it seems to me that in many of these cases the action of the nervous system, like that of Jupiter in ancient mythology, has been unnecessarily invoked from ignorance of the real cause.

One of the most interesting points about gout is the way in which it has been observed to alternate with the troubles produced by collæmia, such as high blood pressure, headache, depression, &c., as mentioned in the chapters treating of these; and this is, no doubt, due to the fact that for some little time round each attack of gout the blood in general is kept relatively free of uric acid, so that severe collæmia is prevented.

Now it seems that there are two chief factors concerned in bringing about this result.

One of these is the fact that uric acid attracts uric acid; and everyone knows that if a few crystals of urate or uric acid are inadvertently left on a urine collecting glass they will increase very greatly from day to day, and every dirty urinal crusted with urates bears evidence to the same fact. And there seems to be very little doubt that precisely the same thing occurs in the body, and that blood or tissue fluid passing near a deposit tends to give up its uric acid to the deposit.

And there is probably another factor as well, as shown by Sir A. Garrod's observation (gout and rheumatic gout Ed. iii., p. 110) that there is no uric acid in the serum drawn over an inflamed joint which led him to suggest that inflammation destroys uric acid.

But as I have pointed out the effect of the inflammation is probably to diminish the alkalinity of the blood and tissue fluids in the inflamed area, hence any blood that passes through this area will tend to leave its uric acid behind it in colloid form, because as we have seen in chapter v. slight acidification of a solution of uric acid in phosphate of soda tends to throw it (the quadriurate) down in colloid form, and this quadriurate so retained eventually becomes a biurate, and is deposited in crystals.

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But if the inflammation lasts only a short time it never becomes a biurate; but remaining in colloid form is quickly redissolved, as the normal alkalinity is restored; and here we see the chief difference between the arthritis of rheumatism and that of gout, *i.e.*, between acute and temporary and chronic and persistent.

It is probably therefore as the result of the action of these two factors that a patient who has for years, perhaps, suffered from headache, mental depression or other signs of uric acid collæmia gets one day, as the result of some strain, blow, injury, or other local cause of alteration in alkalinity, an attack of gout in his toe, and then, perhaps, for several years he has recurrent gout in this toe or other joints, and ceases more or less completely to suffer from the signs of collæmia, but meanwhile he is accumulating a fine tophus in his foot.

Later on some shock, illness, or severe injury depresses him, and then his blood, as already explained, becomes a better solvent of uric acid, and so the gout in the toe ceases, and the collæmia, headache and mental depression return together with an increased excretion of uric acid in the urine.

Later, the same sequence repeats itself, and the collæmia is brought to an end by a fresh attack of gout, and this is the explanation of the well-known tendency of gout and rheumatism to recur and recur often in the same fibrous tissue once they have attacked it, whether this be part of a joint or of the mitral valve, of the pharynx, larynx, trachea, bronchi and fibrous tissues of the lungs or of the cellular tissues in the stomach, intestines and pelvis; for there is left in such fibrous tissue either a condition of diminished alkalinity, or a few crystals of urate as mentioned in chapter ix. or both.

And this completely accounts for the alternation between the symptoms of collæmia and those of arthritis, and the action of cold acids and numerous metals and drugs in changing the former into the latter.

Since the last edition of this book appeared, Dr. Ewart has published a very interesting work on gout,[1] from which the statement of some points may be useful.

Thus, I notice with interest, that from what he says on p. 310, he would agree with me that the assumption of the unknown factor "Diathesis" is unnecessary, and on the next page he says that "marked uricacidæmia and demonstrable deposits of biurates are the features of declared gout."

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[1] Gout and Goutiness. By William Ewart, M.D., Cantab., F.R.C.P. London, 1896.

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But on the other hand he declines to credit gout to mere excess of uric acid, because it (gout) is not a constant phenomenon of leucocythæmia, and does not very often occur in children, whose production of uric acid is so great.

If, however, it be granted that rheumatism is due to urates, and is, as above hinted, by several observers but gout in a child, one of these objections at once falls to the ground; and leucocythæmia is a somewhat rare disease and occurs generally in conditions where there is great depression of nutrition and metabolism, and when consequently the condition of the blood and tissue fluids is, as regards acidity or alkalinity at the very opposite pole to that at which gout occurs; but in the similar conditions of enlarged spleen with or after malaria, with the fluctuations in alkalinity of the fluids produced by recurring attacks of fever, gout is, I believe, not at all uncommon; the leucocythæmia end of the cycle being represented as in the case narrated in chap. ii., p. 43, by attacks of gravel.

Later on he quotes the views of others which make a "depressed and faulty metabolism" the "first departure" and abnormal secretion its result; and makes the goutiness resulting from such faulty metabolism the basis of all articular gout.

He then goes on to mention Horbaczewski's researches, and suggests that increased uric acid production is not largely derived from nitrogenous food though he acknowledges that it follows an excess in nitrogenous diet, but is the result of altered catabolism in the tissue cells owing to their paralysis by excess of nitrogen.

This, however, drives them into the difficulty of explaining why the faulty metabolism persists when the occasioning cause (the excess of nitrogenous food) is withdrawn; and he goes on to attribute this to faulty habit in the tissues partly assisted by faulty innervation.

He blames especially the liver, and congestion and fulness of the portal circulation, but thinks that the faulty habit may be in time replaced by a healthy habit.

Similarly he speaks of the kidney, and says that a renal defect may originate the uric acid trouble, though gout attacks may come on without any obvious kidney trouble, and again granular kidney causes neither retention of uric acid nor gout.

Again following the cell malnutrition theory, he thinks that there may be an inherited goutiness of the whole man, which is there before any articular attacks, and that gout evolves from functional troubles to structural changes.

And again "some structural gouty peculiarities are transmissible

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and may be inherited even by those whose uric acid function is not perceptibly modified: hence uric acid troubles are not the primary cause of the gouty habit" (*loc. cit.* p. 318 and note).

Hence "the history of acquired gout is one of functional disorder leading up to organic lesions, whilst the history of inherited gout is often that of textural delicacy leading to functional disorders."

He then proceeds (p. 319) to refer to the various nervous system theories, but is inclined himself to limit the action of the nervous system to the comparatively insignificant influence which a nervous system may exert on nutrition, as the result of its own failure of nutrition originating in causes outside itself; it is thus merely a link in the causation, not an originator of gout.

It is obvious that with regard to most of the theories here so ably marshalled, I cannot do more than suggest what seems to me a simpler explanation, trusting to the future and its increase of knowledge to strengthen my positions if they are true.

My belief is, and it is steadily increasing and gaining strength, that just as I said at the Medical Society in November, 1896, with reference to headache, "the uric acid diathesis" is a myth; if uric acid is controlled, that is if there is neither excessive introduction nor excessive formation from excess of nitrogen, both gout and gouti-ness would gradually disappear or cease to be evolved, and this is a proposition which in one sense or other can be demonstrated.

I need not here again go into my reasons for believing that depressed and faulty metabolism is a result of excess of uric acid, and not its cause: but I can scarcely follow Dr. Ewart's reasoning in saying that the large excretion of uric acid which follows excess in nitrogenous food is not derived from the food.

It will be seen from my facts and arguments as to Hospital beef tea, in chapter xvii., that a pound of meat from which it is made probably introduces the equivalent (in xanthins) of seven grains of uric acid, and if we credit a man who is taking excess of nitrogen with only half a pound of such meat a day, that would account for an introduction equivalent to 1,200 grains of uric acid in a year, and if he also takes an absolute excess of nitrogen and forms say 100 grains of urea per day more than he has any physiological right to do, he will also form nearly three grains a day of excessive uric acid, or some 1,100 grains in a year.

It is clear then that if such introduction and formation do not account for any excess of uric acid met with in the urine after excess of nitrogenous food, especially in the form of animal flesh, it is not because these will not furnish the required quantity.

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In this connection I will just mention a case I have been told of by my friend, Mr. Hope Lewis, of Auckland, New Zealand. It was that of an hotel-keeper who consulted him for bad temper, worst in the mornings, and general myalgia.

On inquiry, however, it came out that he was most moderate in meat and wine, lived carefully, and ate plenty of fruit, so that Mr. Lewis was at a loss to account for his condition, when the patient said: "I take several cups of beef tea every day; really good stuff it is—my hotel is famous for it." And this is just my own experience, as I often see patients who take little or no meat; but then one is sure to find either that this is made up for in eggs and fish, or that soup, beef tea, or some of the urine-like fluids and extracts so largely advertised, are being taken in its place. Indeed, one almost wonders that the manufacturers of these delicacies do not take a hint from the inhabitants of North Africa and South America, mentioned in chapter iii., p. 107, and obtain a still larger supply of the same products by evaporating urine.

I may just mention here that a butcher at present under my care with gout, Bright's disease, and cardiac failure, acknowledges to consuming two pounds of his own commodities per day; and it is little wonder that urates and their work are visible all over him, or that they have altered his joints[1] and his blood, irritated his kidneys, and dilated his heart, in the manner described in previous chapters.

And now for Dr. Ewart's difficulty as to the persistence of the faulty metabolism after the excess of nitrogenous food has been removed. I believe that the solubility of uric acid suffices to explain it completely. Why the tissues of the above-mentioned butcher are absolutely full of uric acid, and if I were now to put him on a uric acid free diet he would still go on excreting excess of it for months and years, and during the whole of this time he would have the signs of collæmia, with the depressed nutrition and metabolism it produces.

And with the obstructed capillaries of the collæmia and his failing and dilating heart, he would have what we always find with these conditions, congestion of the liver (nutmeg), and of the circulation behind it; so that the poor liver again is blamed for the fault of others, and is not an original sinner.

Exactly the same applies I believe to the kidneys; these organs never, I believe, refuse to pass uric acid unless they are inflamed,

[1] These joint changes are marked, and would undoubtedly be called rheumatoid arthritis if there were no urates to be seen.

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and then they have no choice, as the altered alkalinity of their tissues and fluids affect the solubility of uric acid.

What do we see in migraine while the kidneys are sound? A large excretion of uric acid, though urea may be diminished; but this is simply due to the fact that urea is diminished in the blood, while uric acid is in excess in that fluid.

Similarly in the chronic stages, and absolutely uninflammatory condition of granular kidney, we get, as I have often pointed out, a very large excretion of uric acid, so large that it may considerably raise the specific gravity of the urine and so cut out the diagnosis of granular kidney (see cases in chapter xvi.), or may cause more or less severe symptoms of gravel or calculus, and this because, for reasons already given in this chapter, the blood is full of uric acid.

The kidneys, just as the liver, muscles, skin, and all other tissues are importantly affected by the uric acid, but they themselves always pass out uric acid when it is present in excess in the blood, except perhaps when as in acute Bright's disease, they have their alkalinity diminished, but this is a chemical not a physiological refusal to pass it.

As to inherited gout, I would again ask how much of the inheritance is that of dollars and habits of feeding, and as in the cases of the children, with reference to whom Mr. Hutchinson is quoted at the beginning of the chapter: did they not live in their father's house, and did they not repeat his errors of feeding, both as to excessive introduction and excessive formation of uric acid (*i.e.*, excess of nitrogen)?

Again, as to the faulty metabolism persisting after the excess of nitrogen was cut off, did the introduction of uric acid cease, or were such things as eggs, fish and tea, continued as before, introducing, no doubt, still many grains of uric acid per day?

As to the nervous system, it appears to me to be exactly in the same position as the liver and kidneys, it is sinned against, and the signs it gives are the results of defective circulation, and lesions or irritations of its fibrous tissues.

To my mind, gout is poisoning by animal flesh, with tea and similar vegetable alkaloid containing substances; and the nervous and all other theories have arisen from inability to understand and appreciate the introduction, formation and solubilities of uric acid, and their bearings on the various results produced.

Where the gout attack comes suddenly in the night and is in every way typical, there is not much to be said about the diagnosis,

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and salicylate of soda in sufficient quantity will very quickly relieve it, as in my case in *St. Bartholomew's Hospital Reports*, previously mentioned. It is necessary, however, to give sufficient, and if gr. xx. can be given every two hours for acute rheumatism, I fail to see why it should not, if necessary, also be given for acute gout; certainly neither disease can be expected to yield to a dose of gr. x. three times a day.

Where, however, the attack is not typical, where it is not markedly worse at night, where it is prolonged and chronic rather than acute and sudden in onset, and where it is much worse after exercise, no matter what is the time of day, while true gout is worse at night even though the patient has never moved out of bed all day, we may have to do with traumatic or surgical inflammation, and not with true gout at all. Here salicylates may have no effect whatever, and the proper treatment is by rest and fomentations as employed by the surgeon.

Such inflammation may occur in a joint which has been previously affected by true gout, and may be the result of exercise, pressure, or strain acting on a joint damaged by urates.

This trouble in an old gouty joint is only too easily mistaken for true gout, and when salicylates fail to relieve, the reputation of the drug suffers when the diagnosis is really at fault. Colchicum may then be employed, and, with the aid of rest, the patient is cured.

Now colchicum has this advantage over salicylates, that it does good in both the conditions which are here possibly being confused: it relieves true gout by increasing the alkalinity of the blood and so facilitating the solubility and excretion of uric acid, and it also relieves a surgical inflammation by causing general depression of nutrition, absorption and metabolism, acting in this respect like antimony, aconite or free purgation.

I have seen salicylates fail to cure, but only under conditions where failure could have been foretold.

They are very little use by themselves in chronic rheumatism, and very little more in chronic gout without rise of temperature; again, where alkalies or colchicum have already been used salicylates will not only be of no use, but may do great harm, and again, they are incompatible with the use of hot or Turkish baths for reasons which will appear in the following chapter, and in the descriptions of figs. 62 and 63.

Where alkalies, colchicum or hot baths have been used they had better be continued, unless all treatment can be left off for several days to allow intestinal digestion to recover from the colchicum, and

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the alkalinity of the blood to recover from the effects of alkalies and dyspepsia before the salicylates are given.

In very chronic gout their action may be improved by giving them with sp. am. aromat. or with iodides, or in alternate doses with acids or other substances which raise acidity. And in these chronic cases salicylates may eventually do much good if steadily persevered with, or salicylic acid or the ammonium salt will sometimes succeed where the sodium salt appears to fail. Again, where we have to deal with real uratic arthritis, the local application of salicylate of methyl should not be forgotten. This may be painted on night and morning, and covered with guttapercha tissue and a bandage. It may be used either alone or along with administration of salicylates by mouth. In this case care must be taken not to give too much of the drug, as the methyl salicylate promptly gets into the blood and urine and produces constitutional symptoms, and if painted on too often or over too large a surface these may be severe, but for many local troubles it is by far the best way to use salicylates. And where salicylates by mouth upset the stomach it can replace them entirely.

I may mention here, as it bears specially on treatment, the well-known connection between gout and certain teeth troubles. And indeed, it has been quite a common experience with me that the dental troubles called periostitis, or other inflammation of the pulp or surroundings of a tooth, such as are started by a cold wind in spring or autumn, yield at once and promptly disappear if salicylates are taken for any purpose.

And it seems to me quite possible that we have here again tc deal with a gout of fibrous tissues, originating just like gout or rheumatism elsewhere in the local action of cold, and like these yielding at once to the administration of salicylates.

I have gradually come to use salicylates with the utmost confidence in all such troubles, and I have recently found that their power is so great that the local application of a little salicylate of methyl to the face over the painful tooth and its roots, night and morning or oftener, very promptly relieves and removes such irritation, so that in many cases there is no necessity to administer salicylates internally.

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CHAPTER XVI.

Rheumatism and Morbus Cordis.

Much of what I have said about gout will apply also to rheumatism, and though they can often be clinically distinguished, I do not draw any hard and fast line between them, believing that the arthritis is in both cases due to the irritant action of uric acid on the fibrous structures of the joints.

I have suggested that salicylates cure acute rheumatism by effecting the elimination of urates, and I have further shown that as regards the action of salicin, salol and a salicylate, the latter has most power, dose for dose, in eliminating uric acid, and has also most effect over the arthritis, while salicin has much less effect on uric acid, and requires to be given in much larger doses, and salol is in both respects intermediate between the two (see *Medico-Chirurgical Transactions*, vol. lxxiii., p. 297).

I have further suggested that the action of uric acid as an irritant of fibrous tissues may quite as easily account for the endocarditis and pericarditis of acute rheumatism, as for its arthritis (see *Practitioner* of February, March and April, 1891).

I have also remarked on several occasions, that while the chemistry and physics of uric acid appear to me to be capable of completely accounting for all the phenomena of acute rheumatism, and the action of all drugs and diet that are useful in treatment; as much cannot be said for any other theory of its causation.

For instance, no satisfactory explanation of the value of alkalies among drugs, or of milk and farinaceous diet, or again of hot baths, blankets, and other sudorifics in general management, can be given on the theory that acute rheumatism is due to a miasm or microbe; while on the other hand, a comparatively rudimentary knowledge of the solubility of uric acid and the processes which promote its excretion and elimination will suffice to explain them all.

In reference to these points I have formulated the statement: "All substances which promote the free excretion and elimination of uric acid do good in the arthritis which is due to it, and conversely

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all substances which hinder its excretion and elimination do harm," (*British Medical Journal*, 1888, vol. ii., p. 10). And though, as explained in the previous chapter, some substances which hinder excretion may yet, by keeping the blood clear of uric acid, prevent arthritis, it is quite true that these substances, when first given, are liable to do harm and produce an attack. And again, the pathological condition which most hinders the solubility and excretion of urates (namely, fever) has just the same effects as the drugs which do this, and frequently precipitates an attack of general uratic arthritis; hence we are told by a writer in the *Lancet*, 1893, vol. i., p. 918, that "Enteric fever at its very commencement may present the picture of acute rheumatism." I believe that any acute fever may present this same picture, provided there was in the blood, at the time the temperature began to rise, sufficient uric acid to irritate the joints when it is concentrated upon them; for fever diminishes the alkalinity of the blood, and diminishes its powers of holding urates in solution; and I have already pointed out in chapter xv. that the blood is in this way most completely cleared of urates at the beginning of the fever, which corresponds exactly with the observation of the writer quoted above. And I have myself seen, either alone or with others, several cases in which the onset of enteric fever has been mistaken for acute rheumatism.

The theory that acute rheumatism is an infective disease and due to a micro-organism which causes the production of lactic acid has been prominently brought forward by Dr. Newsholme, in the Milroy Lectures (*Lancet*, 1895, vol. i., p. 589), where he points out that there have been epidemics of rheumatic fever in certain years, and that rheumatic fever is an urban disease more than a rural.

I have always acknowledged that rheumatic fever may be produced by any fever however caused, whether by a specific micro-organism as in the above cases of enteric, or by acute dyspepsia as commonly seen in a schoolboy from (?) natural causes. Anything that diminishes the alkalinity of the blood, and all fevers do this, may produce rheumatic fever if there is plenty of uric acid in the blood at the time.

Now we are liable at many seasons to epidemics of catarrh, influenza, and tonsillitis, not to mention cases of ill-developed specific fevers such as measles, scarlet fever, &c., which are overlooked and pass unrecorded, and any of these may produce corresponding epidemics of rheumatic fever, but there is here not the smallest proof that the rheumatic fever is due to the specific micro-organism and not to the effect of the fever on the alkalinity of the blood.

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And Dr. Newsholme himself tells us that other specific febrile diseases as enteric, scarlet fever, and erysipelas are affected in the same way as rheumatic fever, by season, rainfall, &c.

Exactly so the epidemic of rheumatic fever varies with the epidemic of these diseases because the rheumatism is, to a large extent, the result of these diseases.

Then as to rheumatic fever being an urban disease rather than a rural, this may show merely the relation of acute rheumatism to increased meat eating, which is more common in urban districts, and gout is, doubtless for the same reason, an urban rather than a rural disease; but I have never heard this used as an argument for its being an infective disease.

Dr. Newsholme looks upon throat symptoms as a part of the disease, and the place where no doubt the micro-organism obtains an entrance into the body; but if this is so how does an alveolar abscess serve to precipitate a relapse; or, how does an injury to an ankle or shoulder when the skin is unbroken and no micro-organisms are introduced, serve to bring on acute rheumatism?

In a word, every micro-organism specific or other that produces fever may produce rheumatism, but then there are several other things, not in any way connected with micro-organisms, which will do the same, but all these things—injuries, micro-organisms, and drugs—affect in one and the same way the solubility of uric acid in the blood, *i.e.*, they hinder it and render it insoluble in that fluid.

Again, Dr. Newsholme points out that the tendency to relapse is common to rheumatism and other fevers; but he is also kind enough to allow that frequent relapses occur when animal food is given too early after an attack.

This parallel is little more than skin deep on the surface of the word relapse, for surely a relapse after enteric fever is one thing and a relapse after rheumatic fever another and a totally different thing.

It is surely possible to prevent the relapse of acute rheumatism by continuing the salicylates, or by abstaining from giving the animal food or the iron; but is it possible by any means whatever to prevent the relapse of enteric fever?

Then again, the relapse of acute rheumatism can be produced —is, in fact, generally produced—by some error in treatment. I have seen many such relapses, and knew exactly how they were produced, and so would anyone else who knew anything about the solubility of uric acid, and watched the treatment carefully; and I will undertake to produce relapses in any patient who will consent to its being done.

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Then again, if acute rheumatism is due to a micro-organism, how is it that salicylates cure it (as I have pointed out that they do) in proportion to their power of eliminating uric acid; and I can now also show (see cases narrated further on) that if anything prevents their acting as solvents of uric acid they fail to cure it.

From the other side it would have to be shown that salicylates prevent the growth of the micro-organism; and that iron, lead, mercury, and other metals increase its growth as they make the pains worse.

I shall now pass on to examine the points of difference between rheumatism and gout, and see how far the different conditions under which the uric acid acts at different periods of life will enable us to explain them,

My friend, Dr. A. E. Garrod, who mentions my researches on uric acid in the most kindly manner ("A Treatise on Rheumatism," p. 27), yet objects strongly to my suggestion that acute rheumatism may be due to uric acid. He says: "Many objections present themselves to such a theory of acute rheumatism which appears to me to attach undue importance to the articular troubles, whilst offering no explanation of the occurrence of the cardiac and other visceral lesions of rheumatism." I believe, as I have already said (*Practitioner*, February, 1891, *et seq.*), that uric acid is quite capable of producing all these lesions, and I shall go into the matter presently; and Dr. Garrod goes on: "Again we have the fact that uric acid has not been found in the blood of rheumatic patients, which Dr. Haig explains by supposing that this substance is driven out of the blood into the joints by the high and rising acidity due to the fever; but no deposit of sodium urate is found in the joints. Lastly, it is difficult to believe that the same *materies morbi* is capable of giving rise to two such different disorders as rheumatism and gout."

This last statement is somewhat indefinite, but I hope to be able to show that the differences are those of degree rather than of kind, and that they are due to differences in metabolic activity, in functional activity, or in chemical condition, which affect differently the solubility of uric acid, while the total quantity present also differs in the two conditions.

It has never been a matter of surprise to me that Sir A. Garrod was unable to find uric acid in the blood in acute rheumatism: on the contrary, if he had found a large quantity in the blood, it would have been a death-blow to my theory of the causation of acute rheumatism.

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He does find it in the blood in gout because, as I have previously said, gout is a local disease; in which the acidity of one or two joints is specially raised, and in these all the uric acid that the blood brings in their direction is rendered insoluble and retained, giving rise to irritation and inflammation; but there is no general and complete clearing of the blood from uric acid, except in so far as the specially affected joints take it up.

In acute rheumatism, on the other hand, the conditions are different; there is a general rise of acidity which clears all the uric acid out of the blood, driving it into the joints and elsewhere; little or none remains in the blood because the alkalinity of the whole circulating fluid is diminished; while in gout, though alkalinity generally is diminished, it is only in the specially affected joints that the urate is rendered completely insoluble.

This explains a fact previously mentioned, that when I intentionally produce an arthritis by giving acids, the clinical picture resembles rheumatism rather than gout, because I diminish the alkalinity generally, and drive the uric acid out of the blood into joints and fibrous tissues generally; if I want to imitate gout I must diminish the alkalinity generally, to some extent: but I must also produce local irritation and rise of acidity in a joint by a blow, seton, or other injury, and this will precipitate the uric acid locally, while the blood still contains some.

In further objection to my explanation Dr. A. E. Garrod goes on to say, "but no deposit of sodium urate is found in the joints." He evidently considers the fact that the urate is not found there after death, as equivalent to proof that it has never been there.

My researches have led me to take a very different view, and to believe that even in gout, where urate is retained, so to speak, in mass, and eventually thrown down in crystals of biurate, it may be removed so completely as to leave little or no trace of its presence after death, except the erosions in cartilage, &c., which some weeks, months, or years before death were completely filled up by it.

Much more so in acute rheumatism, where the urates are never present in mass, are only present for a few hours and in the form probably of colloid quadriurate, and produce only a little interstitial irritation. So soon as the acidity which drove them into the joints falls away, and the alkalinity of the blood rises, the urates in the joints are quickly taken up in solution in the blood, and passing through it arrive at the kidney, and are excreted. Hence the excretion of uric acid is, as I have pointed out, directly as the alkalinity of the blood, and inversely as the acidity of the urine, a

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relation which holds both in disease and in health, and can be demonstrated artificially at any time by using drugs which affect the alkalinity. As previously pointed out, Sir A. Garrod suggested that uric acid, when in the blood, is attracted differently by different organs, and that in certain organs, which for various causes are less alkaline than the blood, "the uric acid becomes less soluble and more easily retained." ("Lumleian Lectures," *British Medical Journal*, 1883, vol. i., p. 549.)

If this suggestion be granted, and if it be further granted, as also shown by Sir A. Garrod, that the cartilages and fibrous tissues of joints are both less vascular and less alkaline than the other tissues or the blood (see previous chapter), then the arthritis produced by uric acid is a simple matter of solubility, and can be produced at pleasure to almost any extent, and this, I have good reason to believe, is the case.

But there are other fibrous tissues in the body besides those of the joints, and what is to prevent them from being occasionally less alkaline and from suffering in consequence from a precipitation of colloid quadriurate upon them, and the irritation it sets up?

What about the fibrous tissues in the great lumbar fascia (lumbago), of those that form the sheaths of great nerve trunks (sciatica), and of those again that support the various coats of the intestinal walls (colic), of which I have already spoken, or of the fibrous tissues in the pelvic organs and fascia, especially in women, not a few of whose pains and inflammations in these organs may have an identical pathology with that of gout of the intestines (chapter x.), and that some of these inflammations in women are rheumatic, has, I believe, already been suggested by Dr. Gervis.

But there are fibrous tissues in a more vital organ than any of these, an organ which is sometimes said to be in part analogous to a joint, and is often affected along with the joints in acute rheumatism. I mean the heart.

Will anyone who has looked at a transverse section of the heart wall tell me that the visceral layer of the pericardium is not continuous with fibrous tissue, which fibrous tissue forms the fascia of the heart muscle, and that the fibrous tissue of the endocardium on the opposite side of the wall is not also continuous with the fascia of the muscle in the same way.

Muscles become acid as the result of contraction (Foster, "Physiology," 1877, p. 49), and if in some regions of the cardiac muscle, in proximity to its fibrous investment, the products of functional activity and contraction are not quickly removed,

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the muscle and its adjacent fascia may have their alkalinity so far reduced as to form foci, in which the uric acid circulating in the blood becomes according to our premises "less soluble and more easily retained."

Such retention, also in accord with our premises, giving rise to local irritation, which still further reduces the local alkalinity, more uric acid is deposited, and so on till a considerable area of inflammation going on to proliferation of fibrous tissue and scar formation is the result.

If this may be the effect in the lumbar fascia, why not also in the pericardium and endocardium? The same causes that drive uric acid into the joints and set up arthritis may drive it into the fibrous tissues of the heart and produce endo- and pericarditis.

But as regards the endocardium at least, this is by no means the whole story, as there are causes just such as those which are active in the case of the joints, namely friction and percussion, which may affect its alkalinity also.

Just as in the case of the joints, the heat and friction of exercise often determine which joints shall be least alkaline, and so get the largest share of the uric acid; so in the heart the fibrous tissues of the valves may suffer from friction and percussion, and so be rendered the least alkaline of all the fibrous tissues of the heart at a time when there is a general fall of alkalinity.

Now, the effects of exercise on the reaction of the valves of the heart will be greatest where the work and strain are most severe, this possibly accounting for the incidence of the chief rheumatic changes in the left side during extra-uterine and the right side during fœtal life.

In this way any unwonted exertion or strain on the heart by giving rise to a little local irritation on the opposing surfaces of the mitral or aortic valves may diminish the local alkalinity, cause a local precipitation of uric acid and consequent irritation, and this irritation may, we will suppose, be repeated and repeated till what were at first scarcely visible pin-point nodules of irritated connective tissue, come at last to form well-marked nodules and scars.

Such a process of reasoning helps us to understand how, what is at first a small local irritation in the mitral valve is carried on and on by a frequently recurring uric acid irritation till the whole valve is reduced to the condition of a thickened scar, and we have to deal with the final stages of mitral constriction.

And if, as I believe, an excess of uric acid in the blood obstructs all the capillaries and raises blood-pressure (p. 141), it is

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clear that it must throw increased work on the left side of the heart, first of all on the aortic valves and then during systole, owing to the increased resistance to be overcome, on the mitral valves also; and anyone who has listened to the loud banging of the aortic valves during a uric acid storm (in migraine, for instance) will have no difficulty in realising what I mean.

So that the valves of the left side of the heart are most exposed to injury by friction and percussion, just at the very time when there is an excess of the irritant uric acid in the blood ready to be precipitated upon them should the heat of action cause them to lose for a time their normal alkalinity.

And once a spot has thus become invaded by uric acid the irritation is always liable to be kept up and repeated until a serious and extensive lesion has been produced.

We have then certain conditions to which fibrous tissues of the heart are liable in common with all the fibrous tissues of the body tending to precipitate uric acid upon them, and we have certain other conditions which are common to the fibrous tissues of the heart valves and those of the joints. Can we wonder that the structures are so often affected in acute rheumatism at the same time, and doubtless the liability of the endocardium to friction, percussion and strain accounts for the greater frequency of endocarditis as compared with pericarditis.

With regard to the causes that determine the structures that will be invaded by uric acid, I will quote what Dr. A. E. Garrod (*loc. cit.*, p. 82) says as to the order of invasion of joints: "The influence of external causes in determining the seats of the lesions is far less conspicuous in rheumatism than in gout, but as has been already stated when rheumatic fever follows an injury, the joint nearest to the seat of injury is usually the first to suffer."

Exactly so! the injury diminishes first of all the alkalinity of the affected structures, and then if the injury is sufficiently severe to cause general fever, the alkalinity of the whole body is diminished. The uric acid is first rendered insoluble near the injured structures (hence these are the first to suffer), and later on in other fibrous tissues of the body.

Dr. Garrod also says (same page): "Dr. Fuller has laid special stress upon the liability of joints which have been the seats of local mischief. Dr. Maclagan also regards strain as the most important influence at work in determining the seat of rheumatic lesions, and Dr. Peter Simpson and others have expressed their belief that the joints which are most exercised are specially liable to rheumatism.

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M. Besnier, who is inclined on the whole to agree with them in this opinion, does not think that the rule is sufficiently general for the establishment of a definite law."

There is no necessity to establish a definite law, but every one of the conditions here mentioned can be quite easily translated in terms of uric acid causation.

Joints that have been the seat of local mischief will contain a certain amount of fibrous scar tissue, which, as we know, is very lowly vascular, and this will easily have its alkalinity reduced and very slowly recover it again, and meanwhile uric acid will be accumulated and retained in it.

And the same argument will apply whether the local mischief was in the first instance due to uric acid or external agencies. Once a scar has been produced, uric acid will account for its continued irritation and progressive enlargement.

Thus, suppose a young woman has acute rheumatism, and a few pin-point nodules are left on the mitral valves; she apparently re-recovers from her attack, and perhaps no murmur has been heard, but the valve, nevertheless, has been damaged to the extent of the above nodules, and these form microscopic scars, on which, however, uric acid will be again precipitated at the first opportunity.

And it may not have very long to wait, for, as I have shown above (fig. 30), every woman has more or less collæmia at her menstrual period; and this, by the increased blood pressure it produces, may strain the mitral valve, diminish the alkalinity of the damaged nodules, and then, as the alkalinity is generally diminished at the end of menstruation, clearing the blood of uric acid, and putting an end to the collæmia, some of the urate in circulation may be precipitated upon the mitral valve, especially upon its damaged portions, and increase of lesion results (see pp. 123 and 133).

And when this process is repeated month after month for years, we can easily understand how a microscopic scar becomes at last a leathery and calcareous mass, and why a button-hole mitral is more commonly met with in women than in men.

We can also understand the connection which some have noticed between dysmenorrhœa and certain rheumatoid joint changes: for dysmenorrhœa means a more than usually marked fall of urea and acidity, a more than usually severe collæmia, and consequently more severe and wide-spread irritation in the already damaged tissues of joints or valves.

So that these changes in fibrous tissues due to the irritation of uric acid are more liable to progress from small to great in women

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than in men, and are still more liable to do so in those women who suffer from dysmenorrhœa.

Before leaving this subject I must quote what Dr. A. E. Garrod says (*loc. cit.*, p. 53), on the influence of sex: "Dr. Cheadle has called attention to the greater liability of girls to almost all the individual manifestations of the disease, and my own observations lead me to think with him, that not only chorea, but also subcutaneous nodules, erythema, and rheumatic heart affections, are considerably commoner in female than in male children. It should be mentioned, however, that Hirsch found that rheumatic fever occurred more commonly in boys than in girls under the age of fifteen." From this latter statement we may, perhaps, infer that it is more common in girls after fifteen, when the menstrual influences I have spoken of come into play. In addition to this, the great activity in nutrition and metabolism, when at this time of life girls dash at one bound from childhood into womanhood, must affect the formation and excretion of urates, and greatly increase for a time the possibilities of acute rheumatism, and of collæmia and its various results, and Dr. Cheadle says (*Lancet*, 1889, vol. i., pp. 824 871) that girls of 10-15 years old are twice as liable to rheumatic fever as boys of the same age (see also fig. 51).

I quite agree with the authors quoted by Dr. Garrod, that the joints which are most exercised are specially liable, and believe that it is often possible to tell the occupation of the patients by observing the joints chiefly affected.

With regard to this point, I am indebted to Dr. Aylmer Dumat, of Durban, for the interesting observation that precisely the same relation to exercise holds for the severe myalgic pains which accompany the onset of dengue, and he narrates how both in himself and in patients, an attack coming soon after a long or hard ride was accompanied by pains which were most severe in the adductor muscles of the thighs. He also gives it as his opinion that the feeling of intense fatigue which precedes the myalgic pain is due to uric-acidæmia. It almost seems as if dengue furnishes but one more instance of the power of a febrile epidemic disease, perhaps akin to malaria, or still more to influenza, to produce rheumatism just as is done by the febrile diseases discussed in reference to Dr. Newsholme's theory on a previous page.

As regards physiology, the pains of rheumatism resemble, I believe, those of gout in being worse at night and better in the morning; that is to say, they correspond with the natural fluctuations in the uric acid excretion; though this may be often less

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conspicuous in rheumatism than in gout, as the former, being an acute disease, overpowers for a time the natural fluctuations: and in accordance with this, the first symptoms may occur at very various hours.

The causes which appear to precipitate the attack are just those which would be certain to raise the acidity of the urine and diminish the alkalinity of the blood—thus a chill, getting wet through, or sleeping in a damp bed; the excretion of acid from the skin is interfered with, up goes the acidity, a certain amount of uric acid is driven into the joints, this causes some fever, and the rise of temperature still further diminishes alkalinity and sends the uric acid into the joints.

Temperature in rheumatism at times resembles that of gout in being high at night and lower in the morning; at other times the highest point is in the morning. Of the temperature curves given by Dr. A. E. Garrod (*loc. cit.*, p. 60) of rheumatic fever treated upon the expectant plan, in fig. 1 the highest points are in the evening, in fig. 2 they are for the most part in the morning, and in fig. 5 they are some in the morning and some in the evening, though the morning preponderates.

I think, however, that this is not very difficult to explain, for in rheumatic fever after the first start off (which is due to a very abnormal rise of acidity which may occur at any time, as it overpowers and obliterates the normal curves) the joints have their alkalinity very considerably diminished, and then the only effect of the alkaline tide or its representative will be to bring more uric acid to these joints where it is further rendered insoluble and retained, increasing the irritation in the joints, and so raising the temperature in the morning (see previous remarks in chapter xv., on the causation of arthritis in gout).

As to season. Acute rheumatism is not generally considered to present any definite relationships; and this is in accordance with what I have said, namely, that the attack is often the result of a severe cold or wetting, which may come at almost any season of the year, and that this interferes sharply with the action of the skin, producing a marked fall in general alkalinity which overpowers the natural curves; the only thing that is necessary for acute rheumatism to result is, that at the time of the wetting the blood should contain a considerable amount of uric acid, and this uricacidæmia would for the reasons previously gone into (fig. 4), be most likely to be met with in the spring and summer rather than in the winter, though severe exercise and perspiration would probably produce a

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temporary uricacidæmia at any time, hence the very serious effects of a wetting following close upon these conditions of muscles and skin; and my friend Dr. Eccles, read a paper at the West London Medico-Chirurgical Society (see *Lancet*, 1891, vol. i., p. 1,433) showing that exposure to cold and damp after fatigue, had important influence in the causation of rheumatic arthritis, and mentioned that his experience in over a hundred cases supported my views on the etiology of the trouble. After what I have said about fatigue (figs. 39 and 40), there should be no difficulty in completely understanding this sequence of causation (see also "The Practice of Massage," by A. Symons Eccles, p. 86). As regards experimental work, an arthritis resembling that of acute rheumatism can be produced without difficulty, or when present can be made worse or a relapse can be produced in exactly the same way and with the same drugs as in gout; indeed, as I have said, when one produces a relapse of gout by raising the acidity, the symptoms more often resemble those of rheumatism in that they affect several joints.

In my own person I have often produced symptoms which would, I have no doubt, have been pronounced rheumatism by anyone unaware of their origin.

And in hospital cases it is often quite easy to see how diet, weather, or other independent sources of inflammation produce a rise of acidity (diminished alkalinity) and cause a relapse or aggravation of the rheumatic symptoms. Thus I have related[1] how in a case under my care, a peridental abscess raised the temperature and produced a relapse of the rheumatism; and as I can now see, but did not understand at the time, the action of the rise of temperature was probably aided and abetted by the quinine which I gave for his dental troubles (see "Action of Quinine," p. 44).

The treatment of acute rheumatism by lemon juice (combined, by the way, with plenty of hot water, blankets, and other sudorific treatment) has been supposed by some to be an instance of the cure of rheumatism by the administration of an acid which would be strong evidence against uric acid causation.

But closer investigation hardly bears this out, for first of all, the lemon juice is given with copious draughts of hot water, and the patient is in bed wrapped up in blankets; so that the skin is kept active, and there is a considerable excretion of acids by this channel. Secondly, the effects of considerable quantities of lemon juice on the acidity of the urine is very slight and transitory, as I can vouch

[1] Woods "Medical and Surgical Monographs," February, 1890, p. 355.

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for from my own experiments. On several occasions I took either strong infusion of lemon in hot water, or strong doses of citric acid so far as I thought it safe to go (as citric acid in large doses is a powerful gastro-intestinal irritant), and the result as regards the acidity of the urine was very small (see previous remarks on the effect of taking cider, fruit, &c., pp. 526, 533); on one or two occasions taken from hour to hour, my curves show that it rose a little at first; but the effect on total acidity of the twenty-four hours was little or nothing, and where the lemon is combined with copious hot water and blankets, I have no doubt that the result is a fall of acidity and an increase of the alkalinity of the blood, which will account for the cures it has been said to effect in some cases. On this point Dr. A. E. Garrod says (*loc. cit.*, p. 200): "Dr. Fuller, on the other hand, found lemon juice do good in only three out of a series of twenty-nine cases, and ascribed to it the production of depression, griping, and diarrhœa."

If it produces griping and diarrhœa this would bring about a fall of acidity of the urine, and an increase of the alkalinity of the blood, and might in some cases be of use in this way, just as a drug about which I have previously written, and which has been more in favour for the treatment of rheumatism than lemons, namely colchicum.

Dr. A. E. Garrod says (*loc. cit.*, p. 201): "The extensive employment of colchicum in the treatment of acute rheumatism was doubtless owing to the supposed intimate relationship of rheumatism and gout." My own experience of colchicum showed that it produced considerable intestinal pain and irritation, and as the result of this a fall in urea and acidity, and the falling acidity brought about a plus excretion of uric acid. It should, therefore, according to my rule, be useful in all arthritic trouble which is due to uric acid. About its value in gout there is no dispute, and it is interesting to note, as I have previously remarked, that some have considered that in gout, where it fails to purge, it fails to do good, which is in favour of my argument. In rheumatism it has been, next to salicylates and alkalies, one of the best known treatments, and if I am correct, it really acts as an alkali in the way I have mentioned. But it is indeed difficult to believe that either the lemon juice or the hot water or the blankets have any effect upon microbes.

About cinchona or quinine, opinions are divided, but combined with alkali Sir A. Garrod, Sir Dyce Duckworth and others are in favour of its use. If it is given with sufficient alkali to keep the urate in solution, I think it may do no harm, though its action is, as

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I have said, to produce considerable uricacidæmia; where there is much urate in the spleen, and especially where the spleen is large; and where it produces such uricacidæmia there would probably be considerable headache as its result. Besides this quinine contains a xanthin element, and this will go to increase the available uric acid (see p. 44).

Of alkalies Dr. A. E. Garrod says (*loc. cit.*, p. 203): "The alkaline treatment renders the highly acid urine neutral or alkaline, without causing any increase in its quantity. The blood is found to coagulate more slowly, and the frequency of the heart's beats is considerably diminished." The reason why the urine is not increased and why the heart's beats are diminished is not, I hope, difficult for anyone to understand who has read my previous chapters, and I regard these as conclusive signs that the alkali has produced considerable uricacidæmia, which, under the circumstances, we should expect; and Dr. Garrod goes on: "But the chief claim of this treatment was that it diminished the liability to cardiac implication, and in support of this claim the statistics of Drs. Dickenson, Senator, Chambers and others may be quoted, all of which show a considerably smaller proportion of cases with endocarditis and pericarditis among patients treated with alkalies than amongst those treated by other methods" (see also my case of endocarditis further on).

It is interesting to remember also that those who used ammonia in the treatment of acute rheumatism found that the urine remained acid and the pains severe, but that if alkaline salts of sodium or potassium were substituted the urine became alkaline and the pains were relieved (see Dr. Fuller, *Lancet*, 1862, vol. ii., p. 669, and my paper on the "Action of Salicylates in Rheumatism," *Medico-Chirurgical Transactions*, previous references).

A similar claim of cardiac immunity has now been made for salicylates by Dr. Mitchell Bruce[1] and others, and if the cardiac troubles are due to uric acid it is easy to explain the action in both cases, but it seems to me that no other rational explanation has as yet been suggested. Both drugs have the same action on uric acid, but otherwise they have little in common.

As regards the treatment by salicylates, I have pointed out that the excretion of urate during the first few days of their use in acute rheumatism is enormous, that the excretion is not only absolutely large, as 26 grs. in the 24 hours, but that uric acid bears an

[1] *British Medical Journal*, 1890, vol. i., p. 491.

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abnormally large relation to the urea excreted along with it, as 1—17 in the case which excreted the 26 grs. and 1—14 in the case of a boy of 14 also under my care (see fig. 59).

This figure shows an enormous excretion of urate in the first 24 hours in which salicylate of soda was taken, the absolute quantity being upwards of 26 grs., but taking urea as our standard only 16 grs. of urate were formed on this day (in the relation 1—35). Therefore about 10 grs. of urate came from some source other

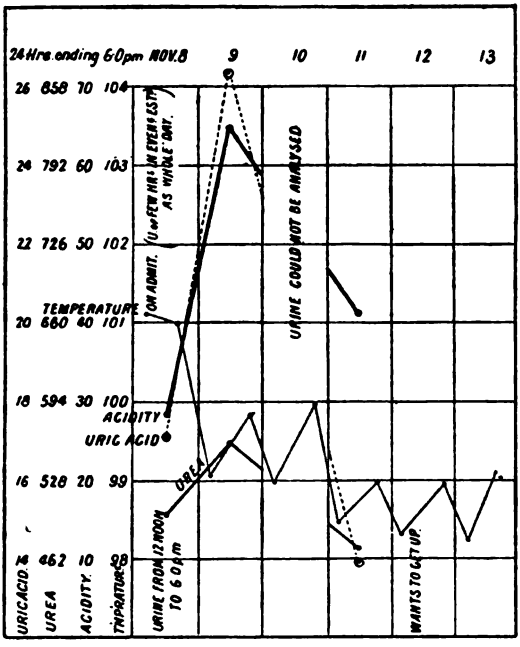

FIG. 59.—CURVE OF EXCRETION OF URIC ACID IN ACUTE RHEUMATISM UNDER SALICYLATE OF SODIUM.

than formation, and probably it was this urate which caused the arthritis, and with its removal and excretion under salicylate there was a marked fall of temperature and amelioration of all the symptoms.

And I have previously suggested that this urate was present in the joints as a quadriurate in colloid form, and that if it had remained untreated or otherwise unremoved, it might have gone on to the deposition of the biurate, crystals of which might then have

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been afterwards found in the tissues: but that as a rule in acute rheumatism it does not reach this stage, and so crystals are not found so frequently or to such an extent as in gout (see also previous remarks on Dr. Mordhorst's researches in chapter v.).

With regard to November 8, the excretion of six hours of the alkaline tide period (all that could be got before treatment) was multiplied by four and counted as a day. This accounts for the slight plus excretion of urate and the low acidity. If the whole 24 hours could have been collected, urate would no doubt, have been far below urea and acidity much higher; this condition of things corresponding with more or less complete absence of uric acid from the blood and the existence of acute arthritic symptoms from its presence in the fibrous tissues.

On November 10 the urine was lost by mixture with another specimen, and on November 11 we see that urate is below urea in spite of 80 grs. of salicylate in the 24 hours. Most of the available urate had been removed on the previous days, and it had nothing to act upon, but with this the temperature is normal and the patient convalescent, and next day he wants to get up.

Compare this with the excretion of urate under salicylate in physiological conditions (fig. 8). The curves are seen to be very similar. The only difference is in the absolute quantity.

Now, in accordance with my premiss that uric acid is never formed in greater proportion to urea than 1 to 35 (see my facts and deductions in chapters ii. and iii.), in both the above cases about half the uric acid excreted under salicylate must have come from some source other than the formation of that day, and I have suggested that this extra urate came from the joints, and that its removal accounted for the subsidence of the pain, irritation, and temperature, and as I have also pointed out the value of the salicyl compounds in acute rheumatism is proportional to their power of dissolving and eliminating uric acid (*Medico-Chirurgical Transactions*, vol. lxxiii.).

In this connection one often hears people speak of uric acid as if it were so much sugar, and as if 10 grs. of it could be introduced, or formed, passed through the blood, and excreted in the urine any day almost any hour, without producing any effects.

Many years of sorrowful experience have completely convinced me that it would be difficult to make a statement which should contain less of the truth.

Even one-half of this quantity, if added on to the ordinary daily excretion and passed through the blood in a few hours, will cause very distinct signs of its presence, such as high blood pressure, head-

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ache, mental depression, dyspepsia, congestion of the liver; and even a fraction of this amount, when driven out of the blood into the joints and other tissues by drugs taken to clear the blood and relieve the above symptoms, may produce pains in the joints which are decidedly uncomfortable, and, if continued for more than an hour or two, may in turn require to be relieved by salicylates.

I must say, therefore, that I do not envy the position of any man who has from four to five times this amount of uric acid in his joints irritating them. I have often had quite as much pain as I could bear with very much smaller quantities (see fig. 65).

Do not let me be misunderstood. I am quite aware that any gouty man may have more than 20 grs. of urate in one single joint, and may suffer but little inconvenience from it; but then such urate is not in solution, but is deposited and lying quiet in the tissues. The condition I am speaking of is that of a man who has 10 to 20 grs. of uric acid driven rapidly out of his blood into his joints, where it remains in strong solution, or colloid form, and with full powers of causing irritation in all the tissues with which it is in contact; such irritation leads on to inflammatory effusion, pressure and tension, and the painful arthritis of acute rheumatism is thus accounted for.

Some years ago Dr. E. Pfeiffer, of Wiesbaden, told me that he had for purposes of experiment injected urates in suspension under his skin, and that they caused pretty decided local irritation.

He then proceeded to take acids and alkalies alternately, and he found that alkalies increased the irritation produced by the urates, but that acids diminished it, and he evidently seemed to think that this was in direct contradiction of my assertion that solvents relieve the pain of arthritis, while drugs which cause retention increase them.

But Pfeiffer's urates were in suspension, and the alkalies increased the pain by getting some of them into solution, and the acids relieved the pain by preventing their solution (see Dr. Mordhorst's results, some of which are quoted in chapter v.).

The urates that cause acute arthritis are in solution or colloid form in suspension, and not crystalline, and they are deposited later on as crystals, and are then comparatively unirritating.

I think, however, that we must bear the point in mind, as it is quite possible that the getting of old urate deposits into solution, as occurs in ordinary old age and the decline of life, may for a time increase the pains.

And this also may to some extent explain the action of drugs of

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the iodide, sulphur and cannabis indica class in relieving chronic gout and rheumatism.

In chronic rheumatism, associated with debility, it seems to me that there is an almost continual excess of uric acid passing through the blood, and every rise of acidity increases the joint irritation; in this case the pains will always be worse at night.

But if there are considerable urate deposits, and the getting of these into solution causes increase of pain, then the pains will be worse in the morning, and then stimulating drugs or diet (such as pure meat diet) which prevent the resolution of these old deposits, will relieve the pains.

I have also pointed out that acids do harm in acute rheumatism, and that cases so treated take a longer time to get well than those which are given only mint water; also that, as observed by others, ammonia which keeps the acidity of the urine high does harm, while soda and potash which lower the acidity of the urine do good, and if we are dealing with uric acid as a cause of rheumatism these facts require no further explanation. An arthritis practically indistinguishable from that of acute rheumatism, and an endocarditis also indistinguishable have been produced, as previously pointed out (*Practitioner*, 1891) by giving and injecting acids respectively (see also cases recorded further on). We must not forget either that, as Sir A. Garrod has shown, urate of ammonium is insoluble, and that ammonium compounds may act like those of lead, mercury, and other metals in clearing the blood of uric acid, and precipitating it on the joints.

I have also pointed out that acute rheumatism is a self-curing disease, that the pain, sleeplessness, failure of appetite and digestion, and the absolute rest which the pain enforces bring about at last a fall in urea and acidity, and that acidity is still further reduced by a considerable excretion of acids in perspiration; so that when the alkalinity of the blood has thus to a considerable extent been restored, the urates are dissolved out of the joints and excreted, and the fever comes to an end, with the production, however, of considerable uricacidæmia, anæmia, and debility (p. 414).

More or less headache and slow high tension pulse are the common signs of this uric acid collæmia, and Dr. A. E. Garrod (previous reference, p. 64) gives tracings of such a pulse in convalescence, while, as I have previously pointed out, Dr. Stephen Mackenzie says migraine alternates with acute rheumatism, and he deduces from this the suggestion that both diseases are nerve storms; but I think that my remark about Jupiter in the chapter

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on "Gout" will apply again here, for migraine we know corresponds with excess of colloid urate in the blood and the rheumatism which alternates with it, with the presence of the same urate in the joints.

In pathology, acute rheumatism may be produced by anything that produces a sharp rise of acidity or fall in the alkalinity of the blood at a time when there is a considerable supply of urate in the circulation (uricacidæmia), but if there is no urate a rise of acidity may produce little or no effect, hence those who eat most meat (see Bouchard[1]) and drink most beer, and have in consequence most uric acid stored in their body, will be most likely to have occasionally considerable uricacidæmia, and when exposure to cold and wet, or the sudden onset of any fever supervenes upon this, acute rheumatism may result.

Now tonsillitis is very commonly a forerunner of rheumatism, and indeed some have claimed it as a part of the rheumatic process, but if this is the case it must often be its only sign, as there may be no other symptom of rheumatism either before or after it.

But tonsillitis is, in my experience, very often associated with conditions of fatigue and over-exertion, and these are just the conditions which might bring about considerable uricacidæmia (see p. 269), and when tonsillitis with fever supervenes upon this, it is hardly to be wondered at that we should have some joint pains or even acute rheumatism.

Influenza again, with its rapid rise of temperature, generally produces some pain in joints and fibrous tissues, and several cases have been recorded in which it has also produced endo- or pericarditis.

A fever, however, has a double action, for supposing that at the time of its onset there is no uricacidæmia, it will not produce any rheumatic symptoms, but as the fever rises the acidity of the urine rises also, and the alkalinity of the blood is diminished, the excretion of uric acid falls below formation, and while the fever lasts a considerable amount of it may be held back in the body, in the liver, spleen, and elsewhere; and when the fever comes to an end and the acidity falls, more or less uricacidæmia will result from the washing out of this stored uric acid. On this let us suppose there supervenes a sharp rise of acidity (from diet, exposure to cold, or the inflammation of any organ occurring as a complication), and acute rheumatism of more or less severity may be the result; that is to my mind the

[1] *Leçons sur les Maladies par Ralentissement de la Nutrition*, p. 241.

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explanation of the rheumatism that follows scarlatina, and may follow other fevers, as measles (see Sansom, quoted by Dr. A. E. Garrod, p. 182, and paper read at the Royal Medical and Chirurgical Society on "Measles as a Cause of Endocarditis, see *Lancet*, 1891, vol. i., p. 880), and compare this with my remarks on the effects of measles on the urine in a case of morbus Brightii, p. 446. The rise of acidity in the fever which cleared the blood of uric acid might, under certain conditions, have driven that urate into the fibrous tissues of the joints or heart; the clearing up of the uric acid collæmia freed the capillaries of the kidney, and profuse diuresis and removal of anasarca resulted. We here, perhaps, see the relationship of nephritis with the chronic collæmia which so often accompanies it, to the disease of the aortic valves, which is not rarely found along with it in the *post-mortem* room (see Dr. Norman Moore, *St. Bartholomew's Hospital Reports*, 1887, pp. 290 and 291), though no doubt the high blood pressure of the collæmia will directly strain the aortic valves.

There is, I think, evidence to show that the acids of beers and wine, and the excessive formation and introduction of urates in a highly nitrogenous diet play much the same part in rheumatism that they do in gout, only in acute rheumatism where the onset is violent, and the sharp rise of acidity is probably due to the action of several causes working concurrently, it is difficult to apportion to each its actual share in the result; but it is well known to be dangerous to give meat, beer, &c., too soon after an attack, and the way in which they tend to produce a relapse is now, I hope, obvious.

And in not a few cases of rheumatism, just as Sir A. Garrod observes to be the case in gout, the effect of giving iron is very promptly to bring about increase of pains and rise of temperature, and in a patient suffering from anæmia recently under my care, who had had acute rheumatism, it was found to be quite impossible to give iron on account of the rheumatic symptoms it produced, and in several cases of what appeared to be chronic rheumatoid arthritis I have had to give up the administration of iron for the same reason, and if the joint symptoms in these cases are due to chronic irritation by urates there is no difficulty in understanding the facts.

Age is a very important point, because it furnishes probably the chief causes of the differences between gout and rheumatism, and I have already pointed out that the condition of the joints is probably very different in the young and in the old.

Sir A. Garrod has shown that the tissues of joints are not only

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less vascular, but are less alkaline than the blood and other tissues, and there can, I think, be no practical doubt that as life goes on, as the arteries become tortuous and degenerate, and as activity of mind and body lessens, the circulation in these joints becomes less and less well maintained, and their alkalinity is not only continually reduced, but slighter and slighter causes will suffice to render them neutral or even acid, and it is this sequence of events probably more than any other which produces the stiff and painful joints so common in the aged, even where no rheumatoid changes are obvious.

So that while the joints of the young are both more alkaline and are better able to maintain their alkalinity, this may, nevertheless, be overcome by a great and general fall of alkalinity, which affects many joints at once, and is due to a powerful external cause (acute rheumatism).

In the old, on the other hand, the joints are less alkaline, and have also diminished power of maintaining their alkalinity; so that comparatively trivial external causes (a slight injury, a little extra exertion, cold, &c.) may diminish the alkalinity of a given joint, especially those of the hands and feet where the peripheral circulation is feeble, and gout results.

And it is extremely probable that uric acid collæmia itself may by obstructing the vessels render the circulation in the extremities less active, and so aid in diminishing the alkalinity of certain peripheral joints, in which the uric acid from the blood is eventually collected and deposited.

But age has an important influence on another factor of uric acid arthritis, namely, the absolute quantity of uric acid that is formed, for while in adults urea is formed in about the proportion of three or four grains per pound of body weight per day, and uric acid in its natural relation of 1—35 would be about ·09 to ·11 gr. per pound per day, in a child of 3 or 4 years old urea may be as much as 9 or 10 grs. per pound, and uric acid ·27 to ·3 gr. per pound.

A child or young person is thus by nature placed much in the position of an adult who eats largely of meat. The daily formation of uric acid is large, and uric acid collæmia and the arthritic irritation, so far as they depend on formation for supplies, are correspondingly easily produced.

It is little wonder then that when young persons who have naturally this extensive nitrogenous metabolism, increase it by eating largely of meat, meat extracts, juices, and essences, the introduction and formation of uric acid should both be very great, and the possibilities of resulting mischief considerable, and that,

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as pointed out by Bouchard (previous reference), children fed on meat and meat extracts should often suffer from gastro-intestinal derangements, skin diseases (see chapters x. and xi.), and early migraine (uric acid headache), and that rheumatism and its most serious manifestations should come early.

It seems to me that if I have escaped from migraine (uric acid headache), by reducing the introduction of uric acid, it is no very extraordinary thing that children whose naturally large nitrogenous metabolism has been increased by inordinate indulgence in meat should suffer severely, and the facts carry their own moral.

Age also influences one or two minor points, which, however may at times have considerable power in precipitating rheumatic (uric acid) arthritis.

One of these is the fact often insisted upon by a teacher of whom I have the most kindly recollections, the late Professor Rolleston, of Oxford, that small animals have necessarily much more surface in proportion to bulk than large animals; for surface increases as the squares, but bulk increases as the cubes of the dimensions. Hence external influences, such as wet and cold, will have proportionally much greater effects on small than on large animals, and wet and cold, as we have seen, raise the acidity of the urine, and diminish the alkalinity of the blood by checking the excretion of the skin (Garrod), and it follows that rises of acidity from this cause will be greater and more powerful in the young than in the old.

Another point is that in children and young persons (probably in consequence of their more active metabolism) slight disturbances will produce great increase of temperature, and rise of temperature means, as we have seen (pp. 83 and 258), rise of acidity, the two things (fever and acidity) being probably co-resultants of increased metabolism; while the extraordinarily rapid development of girls at the age of thirteen (fig. 51) may quite account for their liability to acute rheumatism about that age, as well as to chlorosis and anæmia a few years later.

Young persons then are, from the action of natural causes, often liable to have considerable uric acid collæmia, and whenever external cold or slight febrile disturbance supervenes upon this, a powerful rise of acidity will drive the uric acid out of the blood into the joints and other tissues, for these tissues no doubt share largely in any general fall of alkalinity.

A child with gastro-intestinal disturbance and loss of appetite has a headache and slow pulse, the signs of uric acid collæmia. On this there follows exposure to cold and wet, a slight sore throat, a

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peridental abscess, or other cause of febrile movement, and the resulting fall in alkalinity quickly produces a multiple arthritis with endo- or pericarditis, and changes the picture to that of acute rheumatism.

In this way the production of acute rheumatism may be completely accounted for by the action of causes that are to be met with every day, and the wonder is that any children should escape an attack, but it is fortunately necessary that a good many causes should act together, and this can only occasionally be possible.

Thus uricacidæmia means a large excretion of urate, and where this has gone on for several days the amount in circulation will be reduced. Again, gastro-intestinal disturbance means diminished metabolism and lessened formation of urate, so that unless external cold or febrile movement supervene at an early stage there will not be enough urate to produce the most severe effects on the fibrous tissues. I shall now shortly quote three cases which were under the care of Dr. Savill at the Paddington Infirmary, the notes of which he has very kindly placed at my disposal as they serve to illustrate several of the most important points I have mentioned.

Case I.—John G., age 69, coachman. Admitted February, 1886. Rheumatism and gout very badly for years in knees and ankles. First severe in 1853, in right hand, then in feet, and then general. Father asthma and slight rheumatism, died at 82 years of age.

On admission, February, 1886 :—

Urine 1018. No albumen.

March, 1886.—Much better, gets about fairly well; is taking cod-liver oil.

April, 1886.—Urine 1020. Cloud of albumen.

October, 1886.—Left hip painful, 2 in. shortening and joint disorganised.

November 30, 1886.—Giddy and headache in morning two or three days ago ; better now.

December, 1886.—Much pain in hip. Hands show marked rheumatoid change and distortion of fingers.

1887.—Much the same, giddy on exertion. Pulse compressible, arteries thick. Urine 1008. Trace of albumen.

1888.—Many joints affected; marked rheumatoid changes in hands, elbows, shoulders, knees, and left hip.

1889.—Urine occasional albumen, joints somewhat relieved by soda baths.

1890.—Pains vary with weather, and are worse in east wind. Can walk with the aid of a stick.

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August, 1890.—Urine 1014. Albumen $\frac{1}{6}$. Anasarca of both legs, petechiæ on right.

November, 1890.—Pulse tension plus. Urine 1016. Petechiæ on both legs.

January 6, 1891.—Urine 1012. Alb. large trace.

January 30.—Diarrhœa and collapse. Died 9.15 p.m.

Post-mortem.—Body exceedingly well nourished. Rigor marked. Petechiæ on legs numerous.

Heart.—17 ozs. Left ventricle large. Valves normal. Atheroma of abdominal aorta. Arteries tortuous and thick.

Lungs.—Emphysema and congestion.

Liver.—40 ozs. Hobnail cirrhotic.

Kidneys.—2½ ozs. each. The right contains a cyst as large as a hen's egg. Cortex much reduced. Capsule adherent, surface granular.

Spleen.—5 ozs., capsule thick.

Joints.—Deposit of urate of soda in cartilage of metatarso-tarsal, and metatarso-phalangeal joints of right great toe.

We may sum up the *post-mortem* by saying gout with extensive rheumatoid changes, granular kidneys, cirrhotic liver, hypertrophied heart, and degenerate vessels.

Case II.—Charlotte W., age 62, laundress. Clinical paper headed "Progressive Chronic Articular Rheumatism."

Father died at 70 of rheumatism.

Mother died at 68 of asthma.

Patient had rheumatism first in toes, then in ankles, and then knees.

Admitted July, 1888. An anæmic woman, with enlargement of second phalangeal joints affecting the bone ends. Metacarpo-phalangeal joints also enlarged. Some tilting of fingers to ulnar side.

Left knee much enlarged; very tender on the inner side; brawny œdema of lower part of joint.

Heart.—Systolic murmur at apex and left base. Pulse 90. Artery thick, tense, tortuous.

August, 1888.—Pulse tracing to-day shows a large first wave high up.

Urine albumen $\frac{1}{7}$.

Bullæ forming on ankles.

September, 1888.—Cough and dyspnœa, increasing. Died on 21st.

Post-mortem, September 22, 1888.—Body somewhat emaciated; rigor absent.

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Heart.—18½ ozs. Left ventricle hypertrophied. Aortic valves incompetent, with thick attached borders. Mitral valve slightly thick.

Lungs.—Contain infarcts, with general congestion and œdema.

Kidneys.—Numerous cysts, small, hard, granular. Right 3 ozs. Left 4 ozs.

Liver.—57 ozs., nutmeg, with fatty degeneration.

Joints.—Copious deposit of urate of soda, much erosion of cartilage, tissues around thickened and infiltrated with deposit.

This, then, is another case of gout with extensive rheumatoid changes (diagnosed during life as "Progressive Chronic Articular Rheumatism"), granular kidneys, but to these are added disease of aortic valves, and the condition of the lungs and liver was no doubt secondary to this.

CASE III.—Mary C., age 65. Dressmaker. Admitted January, 1890. Case headed "Progressive Chronic Articular Rheumatism," with gouty history.

Father delicate, suffered from rheumatics in early life.

Mother and one sister died of diabetes.

One brother has rheumatism.

One brother has gout.

Patient had inflammation of the kidneys when a girl, and in 1885 an abscess in the face, which discharged for thirteen months.

The rheumatics came on twenty-seven years ago when she was pregnant, and got worse after her confinement. First came in her ankles and feet.

Did not finally give up work till eight years ago.

Is now able to get about on crutches.

Present condition.—Metacarpo-phalangeal joints seem most thickened and distorted, and their movements are very limited. But all the joints, elbows, knees, ankles are thickened and distorted, and more or less fixed. Ankles seem to be completely so.

Hips and shoulders least involved.

Spine movements impaired.

Skin pale and smooth, not glossy. No fluid in any joint.

Heart sounds normal but feeble.

Lungs emphysema, but natural otherwise.

Urine normal.

March, 1890.—Gets more helpless.

May, 1890.—Urine pale, cloudy, acid, 1028. No albumen.

August, 1890.—Lin. terebin. relieves pain.

December, 1890.—Great pain in right arm.

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Urine 1022. Acid, cloudy. No albumen.

March, 1891.—Suffers a great deal from pains, but they are lessened by lin. terebin.

May 19, 1891.—Face pale. Pain between shoulders and across abdomen. Breathing laboured. Bronchitic sounds front of chest. Bronchial breathing over right upper lobe, and creps. on both sides of back.

Sputum thick, purulent, not rusty.

Slightly better the next day (May 20), but there is bronchial breathing all over left back now.

She died on May 24.

Post-mortem, May 26.—Pleuræ a few old adhesions both sides.

Heart.—12 ozs., substance firm. Aortic cusp of mitral valve slightly thick.

Lungs.—Right 22 ozs. Left 23½ ozs. Considerable consolidation.

Liver.—Pale, fatty, 40½ ozs.

A few small gall stones in bladder.

Kidneys.—Each 4 ozs. Cortex a little diminished. Capsule peeled fairly easily, leaving a somewhat roughened surface.

Joints.—Left great toe. Cartilage eroded. Cancellous tissue exposed. No urate deposit. Left knee similar changes. No urates. Metacarpo-phalangeal joint of right index finger in same condition as great toe.

Here we have extensive rheumatoid changes affecting the same joints in the same way as in the previous cases where urates were found, but there are no urates. Kidneys slight fibrous changes. Heart not markedly hypertrophied. Death from pneumonia.

Here, then we have three most interesting cases, all diagnosed during life as chronic rheumatoid arthritis or progressive chronic articular rheumatism. In two of them urates are found in the joints after death. In the third none.

Now, according to ordinary pathological nomenclature, the first two cases would be called gout, and the third rheumatoid arthritis, but during life they were indistinguishable. There is then some confusion of ideas between clinical medicine and pathology.

I think, however, that my knowledge of the solubility of uric acid enables me to clear up the matter.

From my point of view the joint changes in all three cases were the work of uric acid, but in one of the cases after it had set up the mischief which ended in the more or less complete destruction of

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joints, it was got into solution and passed in the urine, so that at the *post-mortem* none was left in the joints; in the other cases, no doubt, a good deal of urate had been passed in the urine, and if the patients had lived a little longer none would have been found in their joints either, and all three cases would have been called rheumatoid, which is absurd.

It will be observed that the case in which there were no urates differed from the others chiefly in this, that she was much more crippled by her disease than they were. We are told that she had done no work for eight years before admission, and when in the infirmary for the last year or eighteen months of her life her joints were so stiff and fixed that she was practically bedridden.

Now the effect of this helpless condition would be to diminish metabolism. Urea and acidity of urine would steadily fall, the alkalinity of the blood, and therefore its solvent power over uric acid, would increase, and it would become more watery and poor in salts, conditions discussed in the previous chapter, p. 520, and excess of uric acid would be excreted so long as there was any in the body to be got into solution. The liver and spleen would first be cleared, and then gradually during weeks and months the urates in the joints would also be got into solution and passed out in the urine.

And excessive excretion of uric acid was no doubt occurring in the other cases also, as metabolism was probably low in all; but in these cases the plus excretion had been less marked or less continuous, and some urate was left undissolved at the time of death.

It will be seen that Case I. had well-marked granular kidneys, and yet the specific gravity of the urine was, on some occasions, as high as 1018 or 1020. I have very little doubt that on these occasions he was excreting an excess of uric acid, which raised the specific gravity of his urine in spite of his having granular kidneys.

I will just mention a case I was fortunate enough to see in the *post-mortem* room at St. Bartholemew's. It was that of a man, age 41, who had extensive joint-troubles with granular kidneys, endo- and pericarditis. Of his joints, some had urate and others none; thus there were rheumatoid changes in both knees and both elbows, the right ankle, and the right great toe, and there were urates in both elbows, the left knee, and the right great toe. Sir Dyce Duckworth, who was looking at the *post-mortem*, said that seen apart these joints might be called gouty, and those rheumatoid.

This man also had granular kidneys, and if I may trust my

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memory this had not been diagnosed during life because the specific gravity of the urine was too high; doubtless this was due to an excessive excretion of urates, which would have been found if the urine had been examined.

The amount of urate was probably from the action of various causes, not exactly the same in any of the joints to start with, and when the increased alkalinity and watery condition of the blood began to act and remove urate equally from all, the result was that some were cleared before others, for if equals be taken from unequals, the remainders are unequal; hence some joints contained a little urate, others none.

We thus see that the "intimate relationship of rheumatism and gout" is not a supposition but a fact, and a fact founded upon community of causation; that some very simple facts with regard to the solubility of uric acid will enable us to explain all the phenomena and symptoms of both diseases; and lastly, that the failure to find urates in the joints after death is no proof that they have not been there, and produced or assisted in producing the lesions of cartilage and fibrous structures which are found.

With regard to the causation of joint changes it is interesting to note that M. Potain says (*Sem. Med.*, 18th Dec., 1896), that the deformity in arthritis is due to loss of muscle power, which again is due to atrophy of muscle, and that similar changes are found in traumatic arthritis.

We now know a good deal about the causes that effect the solubility of uric acid in the blood and their mode of action; we know also something of its relation to the joints, fibrous tissues, and organs of the body; we know that a large number of drugs which interfere with the solubility of uric acid in the blood appear to precipitate more or less irritation of fibrous tissues and joints; and we also know that everything which we used empirically in the treatment of acute rheumatism—alkalies, colchicum, hot baths and blankets and salicylates—have this one effect common to them all, that they increase the solubility of uric acid in the blood.

So long as we persist in believing that rheumatism is due to some unknown cause, miasm or microbe, we shall continue to say that the patient had an attack or a relapse with endocarditis, which resulted in serious heart lesion and a crippled life, and shall regard these things as inevitable, much as do the jury who bring in a verdict of "death by the visitation of God."

But once we realise that these diseases depend solely upon the quantity and solubility of uric acid in the blood, and that, as I have

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further pointed out, the quantity of uric acid in the blood and its solubility in that fluid are absolutely and completely within our control, we shall pass at one bound from the unknown to the well known, shall see that these deadly diseases are not the result of unpreventable causes, but of our own dietetic follies; and that our children need not be crippled or decimated by them, if we allow them to live according to their own inclinations on milk and garden produce, and abstain from forcing down unwilling throats the stimulating but deadly products of animal metabolism.

For some years past I have been in the habit of asking all rheumatic children I have seen this question: If I offered you a plate of fruit and a plate of meat, which would you take? I have never seen a child that would have taken the meat.

I have already referred to the well-known cases of Sir W. Foster, who, with the object of diminishing the amount of sugar, administered lactic acid to two patients suffering from diabetes, with the result of producing severe arthritis resembling acute rheumatism, and in one of the cases six attacks were produced by repeated administration of the acid.

I have every reason to believe that any acid that is absorbed and affects the alkalinity of the blood will produce similar effects if it is given at a time when there is an excess of uric acid in the blood, and the only point about diabetic cases is that they very frequently have an excess of uric acid in their blood and the high blood pressure it produces, as I have pointed out in chapter xiv., and not only acids, but any drug (and there are many of them) that interferes with the solubility of uric acid in the blood will do the same thing.

Dr. Lauder Brunton speaks[1] of cases in which both rheumatism and endocarditis have been produced by injecting acids into the blood, and he also mentions an instance in which drinking the red wine of Southern Europe appeared to keep up a lumbago from which he was suffering, and that it had often acted similarly in other cases. With regard to endocarditis, he refers to a thesis for the degree of M.D. in the University of Edinburgh, presented by Dr. J. A. MacDougall in 1865, and says that he was able, by injecting phosphoric acid into the blood, "to produce undoubted evidence of endocarditis."

Coming a few years after these remarks of Dr. Brunton's were

[1] *Proceedings of Royal Medical and Chirurgical Society*, April, 1890.

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made, the following case startled me very greatly and made me fear that I had inadvertently caused both rheumatism and endocarditis.

M. J., age 30, was suffering from phthisis of the left apex, with some tuberculous troubles also at the left base. In March, 1894, he had some fresh signs of consolidation at the left base, with a temperature of 102°. After a few days in bed the temperature began to come slowly down, and on March 9, as his appetite was bad and he was a good deal pulled down by night sweats, I gave a mixture containing some nitro-hydrochloric acid and a few minims of liq. strychninæ. On March 10 he complained of pain and tenderness about the left shoulder-joint, increased by movement of the limb; the temperature had risen very decidedly, and on listening over the apex of the heart I was horrified to find a distinct systolic murmur which I had not noticed before. I at once stopped the mixture and gave salicylate of soda in its place, and on March 11 the temperature was lower and the pain in the shoulder had gone; but the systolic murmur remained, and, though I saw him from time to time for six months after this, it never completely disappeared. I have no doubt whatever that I thus caused some arthritis, and I fear also some endocarditis as well.

Since this I have several times seen just such an arthritis of a neighbouring joint (the shoulder) supervene on a gout of the respiratory fibrous tissues, such as is described in fig. 65; and that others have recorded similar experiences is shown in chapter ix., p. 327; and such a metastasis is often a good sign, for as the arthritis gets worse the irritation of the much more important respiratory tissues will diminish.

J. B., age 7, suffering from chorea, was admitted under my care at the Royal Hospital for Children and Women, on October 29, 1894. The temperature on admission was 99·6°, the pulse 80 to 90. I examined the heart, and, finding no murmurs, put her on a mixture containing ℥xv. of liq. arsenicalis to be taken three times a day. On October 30 the temperature was nearly normal, on October 31 it rose to 100° in the evening, on November 1 to 100·6°, and November 2 to 100·4° in the evening. It then kept between 99° and 100°, but on November 6 the pulse had risen to 140 and above, and it remained quick for some time after this; the large dose of arsenic was left off. On November 7 the highest temperature was 99·8°, and liquor arsenicalis ℥iij. was given three times a day. On November 8 the highest temperature was 99·8°, on November 9, 98·8°. From this the temperature remained just about 99° until November 21, when the arsenic was left off altogether. On November 22 a well-marked

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post-systolic murmur was observed at the apex. From this onward the temperature kept about 99°, rising to 100° on December 14, and 100·6° on December 18. By this time the chorea, which had improved markedly on the large dose of arsenic given at first, and more slowly afterwards, was quite gone. She was allowed to get up, and on December 27 she went home, the murmur at the apex of the heart remaining well marked to the last.

With regard to the onset of this murmur, I should say that Dr. Huntley, our very able resident medical officer, believed that there was a very slight systolic murmur at the apex from the first; but that it became more marked while under observation. It is quite certain, however, that I heard no murmur on admission, for my rule is not to give arsenic, and certainly not the large dose I gave in this case, if there is any sign of endocarditis (see remarks on the causation of chorea further on.)

The fairly marked rise of temperature under the arsenic, and its fall later on when it was reduced and left off, point, I think, to some inflammatory trouble in the body, and there was no evidence of any except in the heart; and then the very marked rise in the pulse rate about November 6 may, I think, be taken as pointing to some fresh heart trouble. I may say that my researches show that arsenic, so long as it does not upset digestion, causes a diminished excretion of uric acid in the urine; it will therefore clear it out of the blood, and tend to drive it into the fibrous tissues.

A. S., age 7, was admitted under my care at the Metropolitan Hospital, on February 12, 1895, suffering from broncho-pneumonia, coming on pretty suddenly, with headache and shivering. The temperature on admission was 104°, but it at once began to slope downwards, touching normal on the evening of February 16. On February 17 it rose slightly above 100° in the afternoon and evening, but from that up to February 20 it kept between normal and 100°. On admission dyspnœa was the most obvious sign, and percussion was altered over several portions of the left lung, but a few days later there were more obvious signs of consolidation at both bases (was this a gouty or rheumatic inflammation of the respiratory fibrous tissues causing broncho-pneumonia? and was the subsequent endocarditis a mere spreading of this trouble? See chapter ix.) There was no murmur over the heart and no increase of dulness. On February 20, after the temperature had been at 100° or below it for four days, a systolic murmur was noticed at the apex of the heart, and the cardiac dulness was also found to be a little increased to the right. The temperature now continued for some

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time between 98° and 100°, on February 28 it became subnormal, making, however, daily excursions from 96° to 98°. On March 6 it became more steady and kept nearer the normal, but occasionally ran up to 100°. On March 9 the systolic murmur was still heard at the apex, and reduplication of the second sound at the left base. On March 13 I gave, three times a day, a mixture containing tincture of digitalis ℥ijss., dilute sulphuric acid ℥v., and some glycerine. I gave this because I was not very certain whether the slightly raised temperature and the apex murmur meant endocarditis or not; and, on the other hand, if the murmur was merely due to dilatation, the digitalis might be of some use. As there was some doubt, however, I told the house-physician to stop the drugs

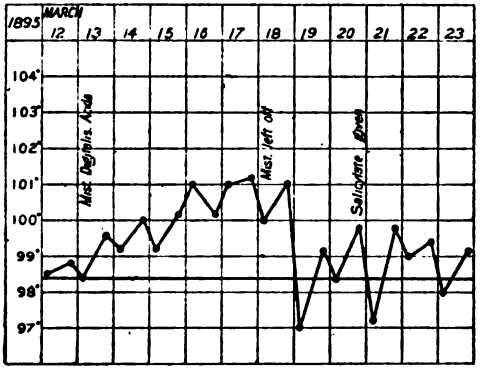

FIG. 60.—TEMPERATURE CHART OF RHEUMATIC ENDOCARDITIS SHOWING THE CAUSE AND CURE.

at once if the temperature rose. Fig. 60 shows the effects produced, and in it we see that on March 12 the temperature ran from normal in the morning to 98·8 in the evening.

On the 13th the mist. digitalis acida was given, and the evening temperature rose to 99·6°, on the 14th to 100°, and on the 15th to 100·2°, and on the 16th and 17th it touched 101° three times, and was never below 100°.

On the 18th the mixture was left off, and though the temperature again rose to 101° that night, it was only 97° next morning, and during the following days never quite reached 100°. The cause being removed the effect began to diminish and disappear; but to aid and quicken its disappearance some salicylate was given on

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the 20th, and on the 22nd and 23rd the temperature began a further steady fall.

If there had been any arthritis I should have said the temperature was due to that, for it rose on the administration of drugs which would have made arthritis worse, it fell when these drugs were left off, and went down still further when salicylates were given. There was, however, no sign of arthritis, but there were signs of its nearest relation endocarditis. The systolic murmur remains, and if anything is now more distinct than before, and can be heard outwards in the axilla. The rest of the history is uneventful; the temperature during April and up to his discharge on May 8 kept between 98° and 100°. The systolic murmur continued, and on April 3 the whole of the first sound was replaced by a murmur.

I have very little doubt that we had here to deal with an endocarditis possibly originating, as I have suggested, in the great strain which falling temperature and its consequent rising blood pressure put upon the valves of the left side of the heart (post febrile uric acid collæmia about February 16 and 17), or as above suggested part of an inflammation of fibrous tissues which was due to urates from the first. That this went smouldering on for some time, and accounted for the irregular temperature which followed convalescence, and then blazed up again at once on the acid and digitalis mixture, for the digitalis not only put extra pressure and strain on the valves of the left side, but the sulphuric acid very probably precipitated some fresh urate upon them.

The temperature fell at once when these drugs were left off, and became still more steady when salicylates were given, but the local irritation went on smouldering as before, though before he went out his temperature had been practically normal on several occasions for a few days.

This chronic irritation of fibrous tissues with little or no fever (I may remark in passing) is exactly the condition in which salicylates will not completely cure; but in which a uric acid free diet may be expected in the course of a few months to completely extinguish the smouldering disease, a disease which under ordinary diet is practically certain to go on for years with slowly increasing lesions till death ends the scene. Indeed, it must be evident that while urates and xanthins are being constantly poured in day after day in the food, neither salicylates nor anything else can keep the tissues completely clear of them.

For comparison with fig. 60 I will now give fig. 61, the temperature chart of a patient, Amelia M. J., age 21, admitted under

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my care into the Royal Hospital for Children and Women in March, 1897.

Her history showed that she had had diphtheria badly in 1895, and rheumatic fever in November, 1896, being seriously ill and in bad health ever since.

Examination of her chest showed obvious hypertrophy and dilatation, with well-marked evidence of mitral disease and some doubtful evidence of trouble at the aortic orifice also.

Her temperature on admission was 97·6° and her pulse 114, decidedly irregular both in time and force.

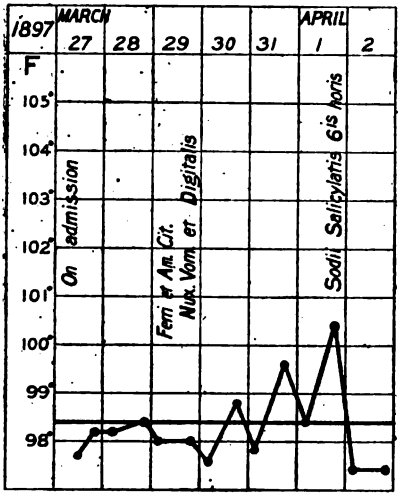

FIG. 61.—TEMPERATURE CHART OF RHEUMATIC ENDOCARDITIS. ANOTHER CASE.

As the temperature remained subnormal on the day of admission and on the following day, I ventured, on March 29, to give her some nux vomica and digitalis, for which there were all the usual indications, these being added to the mist. ferri et am. cit. of the hospital.

We had thus in this mixture three drugs which would tend to retain uric acid in the tissues and make arthritis worse, namely, the iron, the ammonium, and the nux vomica; and the digitalis would probably raise the blood pressure and put some little extra strain and tension on the valve structures of the left side.

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But there was no sign of endocarditis, for the temperature was subnormal and the pulse was quick, and gave all the signs of heart failure; and though the rheumatic history was recent, the fires of inflammation seemed to have quite died out.

It was therefore a surprise to me to find that on the evening of March 30 the temperature rose to 98·8°, and on the evening of the 31st to 99·6. Accordingly, on April 1 I stopped the mist. of March 29 and gave salicylate every six hours.

The temperature rose that evening to 100·4°, as the salicylate had not had time to come into action, but fell next morning to 97·4°, and never rose again above normal.

I have here again no doubt whatever that the drugs given relighted a smouldering rheumatism of the heart valves, an endocarditis which, owing to the serious valve lesions and the depression produced by very defective circulation, had given but little sign in the temperature chart.

These figures seem to me to speak for themselves, and to demonstrate the causation of a relapse of endocarditis by drugs which clear the blood of uric acid at the same time that they put pressure and strain on the fibrous tissues involved.

And I should take this view of the matter even if I did not already know that I can produce at any time a relapse of arthritis in anyone who has previously suffered from it with these same drugs or with others which act in the same way.

While speaking of these cases I will just mention the suggestion of my friend, Dr. Theodore Fisher, in a most interesting article (*Lancet*, 1896, vol. ii., p. 170), that Dr. Caton's treatment, by rest, and iodides with salicylates, and local blisters, of which I shall speak further on, cures such cases, because 40 days' rest in bed allows dilated hearts to recover themselves.

In the case of which the temperature is given in fig. 60, rest in bed for nearly three weeks produced no obvious effect on the heart's condition, and the administration of drugs that would probably have done good for a dilated heart, but which would have caused arthritis in anyone who had previously suffered, at once sent the temperature up and probably aggravated the heart lesion.

I mention this here merely to suggest that where, as is often the case, there is great difficulty in the diagnosis between dilated heart and endocarditis, perhaps standing, as in the case of A. S., entirely alone and apart from any arthritis, some of the drugs used in these two cases (figs. 60 and 61) should be given, for if we have to deal with a dilated heart its condition should improve under this treat-

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ment and the temperature should remain steady; while if there is recent smouldering endocarditis, the temperature will at once run up as in these figures, and its careful treatment with salicylates followed by diet is indicated. I may say also, in this connection, that I am quite unable to agree with the remark of Jaccoud (*British Medical Journal*, Epitome, 1896, November 28, p. 88) that salicylates are contra-indicated in rheumatism with visceral lesions, that is, if these include endocarditis.

I should acknowledge that severe visceral lesions, by upsetting the nutrition and metabolism of the whole body, often produce conditions which are unfavourable to the best action of salicylates, to which I shall have to refer when speaking of fig. 62; but I am decidedly of opinion that in conditions of acute endocarditis, such as we are probably dealing with in figs. 60 and 61, there is no better drug than a salicylate, which, if it cannot be taken by mouth, should be applied to the skin as salicylate of methyl.

In chronic endocarditis without rise of temperature, these drugs, just as in chronic arthritis, are comparatively of but little use; and here diet will, I believe, be found to yield more and more frequently, the oftener it is resorted to, the most satisfactory results.

L. G., age 45, was admitted into the Metropolitan Hospital on January 22, 1891, suffering from gout in the fingers of the right hand. He had gout first in toes and instep in 1882, and since that in the fingers, toes, ankles, or knees. The pain and swelling in the fingers, which were swollen, tense, and shining, began two days before. Temperature on admission 101°, rose at night to 102°. He was given a mixture containing gr. xx. of salicylate of sodium four times a day. On January 24, the pain in the fingers had ceased. The temperature fell in the evening to 99·6°. After this he went on well, and the salicylate was left off on February 7. On February 9 and 10 he suffered from pain due to an alveolar abscess. On February 11 the temperature rose at night, and there was some return of the gout in the fingers and in the bursa of the olecranon process on the left side. On the morning of February 12 the temperature was 100·4°; the teeth stumps were extracted and some salicylate given again, and the temperature soon fell to normal and the pain went.

Note the speedy relief of gout by a salicylate; in my experience it relieves all arthritis due to uric acid, provided that it is fairly acute, which means that the alkalinity of the blood is low.

I have already mentioned the case of a boy where similar teeth trouble brought about a relapse of acute rheumatism; and I

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have also seen a case where the fever of an attack of pneumonia produced a relapse of gout in a patient who had had previous attacks.

E. S., age 36, admitted into the Metropolitan Hospital on December 31, 1894, suffering from acute rheumatism; had been confined nine weeks before (for the effects of parturition on uric acid, see p. 128). The pains began three weeks before admission, first in the head and then in the limbs, shoulders, knees, wrists and elbows in that order. The joints were all very tender. The temperature was 102°. She was given a mixture containing salicylate of sodium gr. xv. and bicarbonate of potassium gr. x. to be taken at first every two hours. On January 2 the temperature was 100°, but the joints were still tender. The bicarbonate of potassium was omitted from the mixture. The temperature ran up that night to 102·8° (the highest it had been since admission), and there was a sharp return of all the pains. It fell to 100° the following morning, soon went down to normal, and never rose again.

Now what was the meaning of this sharp and sudden relapse when the drugs were altered? Was it due to the untamable microbe? I believe it is in my power to show that it was simply and solely a matter of the solubility of uric acid, for I have observed the same thing before under similar conditions.

Some years ago I had under my care a patient suffering from subacute Bright's disease whom I had put on admission on a mixture containing citrate of potassium. After she had been on this for several days she got some pain and swelling in several joints, so I stopped the potash salt and put her on salicylate of sodium, and in a few days her pains were very much better, and the salicylate was therefore left off and the potash mixture resumed; here again, just as in the case of E. S., there was a sharp but temporary return of all the joint pains as the result of the change of drugs.

It seems then quite clear that when arthritic pains are being relieved by a salicylate it will make them worse to add potash, and, conversely, when arthritic pains are being relieved by potash, it will do harm to add a salicylate. My own personal experience quite bears this out, for when some years ago I had my uric acid under less perfect and complete control than at present, I used occasionally, after severe exercise in hot weather, to get some pain and stiffness in the fascia either of the neck or the lumbar region; and I often found that these troubles were completely removed by a few doses of salicylate of sodium, so long as I kept quiet and cool in the house in the morning; but if in the afternoon I went out and got overheated, still

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continuing the salicylate, my pains returned, and were worse—perhaps much worse—than if I had taken nothing.

Now what is the effect of going out and getting hot? It has been shown by Sir A. Garrod and myself that it produces a fall in the hourly excretion of acid in the urine—say the hourly excretion of acid in any individual is equal to 3 grs. of oxalic acid, then going out

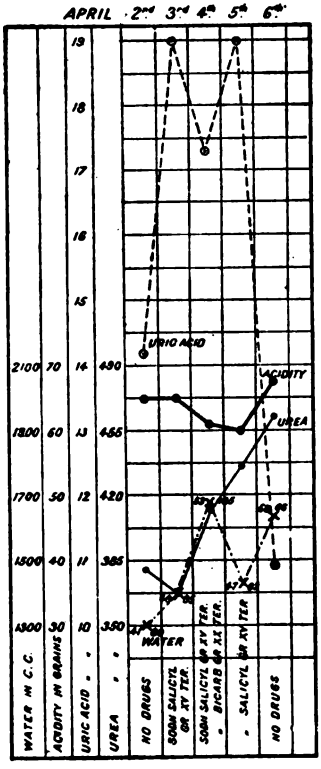

FIG. 62.—EFFECTS ON EXCRETION OF URIC ACID OF GIVING BICARBONATE OF SODIUM WITH SALICYLATE OF SODIUM.

and getting very hot will, other things being equal, reduce it to 1½ or 2 grs. in the following hours; that is to say, getting hot is equivalent to a dose of alkali.

But we have already seen that alkalies and salicylates do not pull well together, and we know that uric acid may be excreted in excess under alkali or under salicylate, and it must be extremely annoying to preconceived opinions that giving the two together does not pro-

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duce the best effect of all; but unfortunately it does not, as can be proved by experiment.

Fig. 62 shows the effect of taking in physiological conditions a mixture of salicylate and bicarbonate of sodium, and before proceeding to describe it, I must point out that in all ordinary curves of excretion under salicylates, the drugs being continued day after day in the same dose, the excretion of uric acid rises to its highest point on the first or second day that the drug is taken, and after that, however long the drug may be continued, it will never again rise to the same height (see p. 38).

But in fig. 62 we see that the excretion of uric acid under salicylate of sodium rose to 19 grs. on April 3, fell to 17¼ grs. on the 4th, and rose again to 19 grs. on the 5th; we have here then an excretion which is quite different from that of the ordinary excretion of uric acid under salicylates.

On April 2, no drugs were taken, acidity stood at 65 grs. of oxalic acid, and uric acid exceeded its usual relation to urea in formation by some three grains.

On April 3, 15 grs. of salicylate of soda were taken three times a day; acidity remained at 65 grs. of oxalic acid and uric acid rose to 19 grs. or 8½ grs. above urea.

On the 4th the same dose of salicylate was taken and gr. xx. of bicarbonate of sodium were added to each dose.

Acidity fell to 61 grs. and uric acid fell to 17¼ grs.

This might be but the ordinary curve of excretion under salicylate, in which case uric acid might be expected to fall still further on the 5th.

On the 5th the same dose of salicylate is taken; but the bicarbonate of sodium is left out: and with this uric acid does not fall, on the contrary it rises to 19 grs., the same height as on the 3rd.

On the 6th no drugs are taken, and the natural result is that uric acid falls down considerably below urea which has been rising for some days.

It seems to me then to be perfectly clear that there was something on April 4 which interfered with the normal excretion of uric acid under salicylates, and that the bicarbonate of sodium and the fall of acidity it produced, in spite of a rise of urea, were the cause of this, and that if from the 3rd to the 5th salicylate alone had been taken we should have had on the 4th a rise to 20 or 21 grs., and on the 5th a marked fall to 15 or 16 grs.; but as it was the amount of urate held back on the 4th enabled the excretion to rise to 19 grs. again on the 5th.

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I conclude, therefore, that the mixture of salicylate and bicarbonate of sodium is unfavourable to the excretion of uric acid, and produces less excretion than the same dose of salicylate given alone.

I have previously referred (see p. 36) to the chemical composition of salicyluric acid and what is known about its solubility, and have suggested that this might be found to explain the result, but clinically the facts are of far more importance to us than their chemical explanation.

Now it is well known that salicylic acid compounds act best in acute arthritis, and better the more acute the case and the higher the temperature; and it is a matter of the most simple observation that the higher the temperature the higher the acidity of the urine, the greater the hourly excretion of acid, and the less the alkalinity of the blood; therefore salicylates act well when the alkalinity of the blood is low.

It is further known that in subacute cases with but little rise of temperature salicylates may act far less satisfactorily, and I have pointed out that in such cases their activity may be increased by giving them along with substances which raise the acidity or in alternate doses with an acid; therefore salicylates act badly when the alkalinity of the blood is high or undiminished.

It appears, then, that uric acid in the blood may be in solution either with a salicylate or with (potash or soda) an alkali, but it cannot be in solution with both at one and the same time; and that if it is in solution with an alkali and a salicylate is added this will diminish the alkalinity, and hinder the solubility of uric acid under an alkali; but until the alkalinity has been very greatly reduced the uric acid will not pass into solution as salicyluric acid, that is to say, between the two drugs there is a dead point at which the uric acid is not in combination with either, but is rendered insoluble, and driven out of the blood into the fibrous tissues of the joints or fascia, producing a relapse of the gout or rheumatism, and a rise of temperature. If the salicylate is continued the alkalinity falls still further, and then salicyluric acid is formed and got into solution, the uric acid passes freely in this form from the joints into the blood, the temperature falls, and the pains subside once more.

Now, what occurred in the case of E. S. was that she was being given a considerable amount of potash along with some salicylate and her urates were got into solution with potash and little or not at all with salicylate; but when the potash was left off the alkalinity fell, the potash lost its hold over the urates before the salicylate gained it, and the urates were for a time driven out of solution into

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the joints and fibrous tissues, producing a sudden relapse of all her pains, and a temperature of 102·8°; later on, the salicylates had it all their own way, and there was no further joint irritation or rise of temperature. This shows, I think, that salicylates control the pain and temperature of arthritis simply by eliminating uric acid; if anything prevents their eliminating uric acid the pains promptly return, and the temperature rises in spite of them.

I have been told a fact of great interest in this connection by Dr. W. Goodson, of Stratford, E., namely, that his stock mixture of salicylate always used to contain bicarbonate of potash, but one day the potash salt ran short and acetate of ammonium was put in its place, and this has been continued ever since, as it was soon found that the effects of the mixture in curing rheumatism were greatly increased. A little later Dr. Goodson came on this book and there saw the probable explanation of what he had observed.

While speaking on this subject I may mention that I have been told of a practitioner in India who refuses to call much of the arthritis he sees rheumatism, because salicylates do not relieve it; but this, if I am right, is exactly what I should expect, for salicylates will not relieve rheumatism even in this country when the weather is very hot and causes much perspiration, and Prof. Latham has remarked (*Medical Magazine*, March 1895), that salicylates act best when the patients are kept cool (see also article by the author on "Gout and Rheumatism" in the *Medical Annual*, 1897).

The fact that salicylates fail to relieve arthritis in a hot climate is no proof that the arthritis in question is not rheumatism or not due to uric acid, but merely shows that the practitioner who would draw such a conclusion is ignorant of the *modus operandi* of salicylates, and the chemistry and physiology that condition it.

On the other hand, I have seen salicylates given in various local and traumatic inflammations and in pyæmia, and their effect on the pain and temperature was just nothing, because these were not due to uric acid. Further, I have pointed out[1] that the compounds of salicin and salicylic acid are powerful in the relief of acute rheumatism exactly in proportion to their power over the solubility and excretion of uric acid; and that those that have least power of elimination (such as salicin) must be given in much larger doses than those (such as salicylic acid) that have most. I make bold to say that every drug that has ever been used with benefit in acute rheumatism in the past, and every drug still to be discovered

[1] *Medico-Chirurgical Transactions*, vol. lxxiii., p. 297.

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that may be used with benefit in the future, will be found to do good in direct proportion to its power of eliminating uric acid in the urine.

I shall now shortly mention one or two cases in which a relapse of chronic rheumatism was produced by drugs given for other purposes.

T. P., age 71, was admitted into the Metropolitan Hospital on January 14, 1895, suffering from chronic rheumatism (? gout). He had had an attack ten years earlier of sciatica, and, two years later, arthritis in both hands. This he had had off and on ever since, chiefly in the legs, but the hands were a good deal distorted and crippled. He was ordered salicylate of sodium and given some cod-liver oil. He improved steadily, and was soon able to walk much better, and had little or no pain. The temperature varied from 97° to 99°. On February 5 he had some little bronchitis, the salicylate was stopped, and he was given a mixture containing ammonia and senega. As the pain returned the ammonia mixture was stopped and the salicylate resumed on February 9. On February 13, the pains were distinctly better, but the salicylate was kept on, and, as the previous dose was small, it was increased to gr. xv., and the improvement was steady and continuous. We have here only the patient's word for it, as the temperature showed nothing, but there was no reason why he should have complained of more pain just at the time the drugs were altered.

H. K., age 66. This case very similar to the above, was suffering from chronic rheumatism and sciatica. He was admitted into the Metropolitan Hospital on January 15, 1895. There was a history of having suffered for nine years. Pains were now chiefly in left knee and hip. He also was put on salicylate, and improved considerably, but he also later on got bronchitis, and on March 20 was given the same ammonia mixture as in the other case. On February 23 the note says: "Can get about better, and pain is, comparatively speaking, gone." On March 20 he got some bronchitis. The salicylate was stopped, and mist. senegæ cum ammonia ordered. On March 26 the pains were decidedly worse again, especially in the knee. He was ordered to have the salicylate mixture as well as the ammonia, and the pains soon got better.

I have already said that urate of ammonium is one of the more insoluble urates, and that ammonium raises the acidity of the urine and increases the hourly excretion of acid. It would therefore increase gouty or rheumatic pains when given alone, but would not interfere with the action of salicylates, on the contrary would aid it (see previous observations on this point).

I could easily give a number of similar cases; indeed, a week

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never passes without my seeing one or more of them. Almost every time a uric acid headache is cured some joint pains are produced, and in gouty and rheumatic cases the well-known effects of changes of weather can almost always be translated into changes in the alkalinity of the blood, secondary to the effects of the weather on the excretion of the skin.

Thus a patient recently seen gives me the following history of an attack of gout. He lives in India but occasionally comes home to England, and after a previous visit to England, where he had been "feeding up," he felt the heat very much in the Red Sea on the way out, and then in Bombay was exposed to comparatively cold March winds, and had a violent attack of gout. Can anything be more simply and easily explained than this history? We have (1) the ingestion of a lot of uric acid, (2) its solution in blood (uric-acidæmia) as the result of heat, and (3) its precipitation in the joints by the rising acidity produced by cold winds.[1]

Similarly in patients who suffer from mental depression, pains in the joints are often looked upon as the harbingers of better things; and in women, when menstruation with its depressing influences causes a rise in the alkalinity of the blood and an excess of uric acid in that and the urine, mental depression or headache are generally worse, while rheumatic pains are to some extent relieved (figs. 30 and 31).

The effect of change of weather is largely dependent on change of temperature, and we have seen that this regulates the loss of acids in the form of perspiration, and so determines the alkalinity of the blood and the acidity of the urine. Thus exercise with perspiration (see chapter viii.) lowers the acidity of the urine, increases the alkalinity of the blood and floods it with uric acid.

It follows that heat in any other form, as hot air baths, hot water, Turkish baths, or hot applications of any kind, provided that they affect a sufficiently large surface, will similarly influence the alkalinity of the blood, the acidity of the urine, and the excretion of uric acid.

Now, fig. 63 shows the effect of a Turkish bath on the acidity of the urine, and I give it here because it has an important bearing on both the causation and the treatment of rheumatism.

In this figure the upper curve marked N is a reproduction of the curve of urinary acidity in fig. 3, while B shows the effect of the bath on the excretion of acid in the same hours.

[1] See *British Medical Journal*, 1895, vol. i., p. 640.

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At 5 p.m. B was slightly above N, and at 6 p.m. below it, and the net result of these two hours before the bath is that B is lower than N by about $\frac{3}{8}$ to $\frac{5}{8}$ grain per hour.

In the hour ending 7 p.m. the Turkish bath was begun, and it came to an end in the hour ending 8 p.m. Supper was taken and finished in the hour ending 9 p.m., this being exactly the same hour as in fig. 3.

We see, then, that from the time of the bath, 7 p.m., up to 10 p.m., there is a steady divergence of the two curves, N rising while B falls, so that at 10 p.m. B is $1\frac{1}{4}$ grain below N.

At 11 p.m., however, they come much nearer together, but this was due to a rise of B while N remained unaltered. At 5 a.m. they

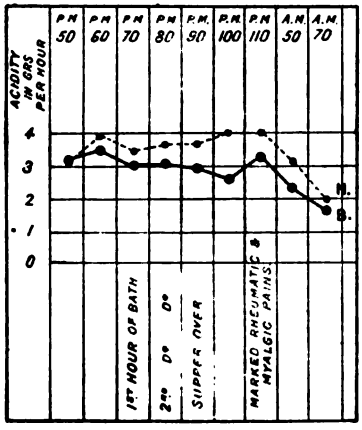

FIG. 63.—EFFECTS OF A TURKISH BATH ON THE ACIDITY OF THE URINE FROM HOUR TO HOUR.

are just the same distance apart as at 11 p.m., but at 7 they are again very close together.

In the hours 7 p.m. to 11 p.m. inclusive, N exceeds B by almost exactly 3 grains, if we make no allowance for the fact that B was a little below N to begin with; or if we allow $\frac{3}{8}$ grain per hour for this, then the effect of the Turkish bath was to diminish the excretion of acid in the urine by 2 grains in those hours.

But this fall in excretion of acid, small though it seems, was the index of a very distinct effect on the alkalinity of the blood and on the excretion of uric acid, for when the rise of B occurred in the hour ending 11 p.m., there were very marked myalgic and rheu-

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matic pains in several parts of the body, which no doubt showed that during the previous hours there had been some excess of uric acid in the blood, and that the fall of alkalinity was now causing it to be retained in the fibrous tissues.

Practically, the bath depressed the acidity of the urine for twelve hours, the greatest effect being shown in the two hours that immediately followed it, and there can be no doubt that a similar bath repeated every day for a week would have a very distinct effect on the alkalinity of the blood and the excretion of uric acid, and would thus have probably a very distinct effect on any arthritis that was due to uric acid.

The first effect of such a bath would be to increase the excretion of uric acid and relieve the pains of arthritis; but later on, when the alkalinity of the blood began to fall again, as at 11 p.m., some urate would again be driven into the joints, and the pains would be increased; and this increase of pains would be very marked if a patient, after a bath, unwisely exposed himself to cold and damp, which would quickly check perspiration, or drank acid wines, which would also diminish the alkalinity of the blood.

The case of J. B., mentioned above, in which the treatment of chorea by large doses of arsenic seemed to produce or increase an endocarditis, almost raises the question of the causation of chorea, for unless there was some excess of uric acid in the blood along with the chorea, the arsenic would not have produced an endocarditis; and this suggests the further question, does arsenic cure chorea by clearing the blood of uric acid, or is chorea one of the effects of excess of uric acid in the blood?

And there are a few facts in this connection which it may be as well to bear in mind, even though they do not as yet justify any definite conclusion.

First, then, chorea has a fairly definite relation to acute rheumatism, and this relation seems to be that it precedes or follows it, but does not often accompany it.

Now migraine bears just the same relation to rheumatic fever (see p. 565), and migraine is due to uric acid collæmia.

Again, chorea, like migraine, comes along with conditions of dyspepsia and debility, in which it follows from our first principles there is certain to be an excess of uric acid in the blood.

Then, again, the mental condition in chorea, the dulness, inability for work, and the increase of irritability, are these not also the symptoms of collæmia?

The late Dr. Sturges considered that chorea was an exaggeration

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of fidgetiness, and is not fidgetiness a sign of collæmia in not a few gouty adults?

Then chorea has been said by Dr. Dickinson and others to be due to widespread hyperæmia of the nerve centres, and Dr. Handford (*Brain*, 1889, p. 129) has pointed out that overwork produces such congestion of centres and tends to make it persistent, and that this condition of centres is evidenced in adults by trembling of hands, nervous starting, twitching of orbicularis palpebrarum, and fidgetiness; but overwork (fatigue), as we know, also produces collæmia.

Then, again, chorea is not very distantly related to the tremors of the aged and feeble, and I observed a good many years ago that these tend to be worse in the alkaline tide hours of the day, and I gave acids with the object of diminishing them, in some cases with apparent success.

Dr. Handford also mentions a case where chorea began during menstruation which followed mental depression and hysteria, and in this case embolism and thrombosis of certain vessels were found at the *post-mortem*.

Then, again, chorea often follows shock, fright, or emotion, and these conditions, as we know, often suffice to depress the metabolism of the body and produce collæmia as the result of the depression.

And, if chorea is the result of hyperæmia, stasis, or thrombosis in certain nerve centres, it is not difficult to see how the obstruction of capillaries by uric acid in the way previously suggested may account for this.

Then as to the drugs which cure chorea, arsenic probably clears the blood of uric acid, and I have suggested in the above-mentioned case that it produced endocarditis in doing so.

Antipyrin appears to have been used with advantage by some (*British Medical Journal*, 1894, vol. ii., p. 1,227), and it also cures migraine.

Lastly, salicylate of soda may do harm in chorea and make the movements much worse, and though salicylates do no harm in migraine when given at the right moment, they may make it much worse if given wrongly, *i.e.*, at a time when there is much gastric upset with debility and depression.

Under these conditions they bring excess of uric acid into the blood, and if the blood is strongly alkaline owing to dyspepsia and debility, the uric acid will combine with the alkali and make the migraine much worse; and this is the reason I first use mercury in migraine to clear the blood of uric acid, and set things going upwards, and then follow it by salicylates to carry off the uric acid.

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I can easily understand, therefore, that salicylates may make chorea worse, for it is so commonly associated with conditions of debility.

We see then that there are numerous connections between chorea and collæmia, and that if chorea is due to collæmia we can at once see the explanation of its relation to acute rheumatism, which is similar to that of migraine.

Chorea, therefore, may be but a variation of migraine, the uric acid collæmia and its circulatory disturbances producing more serious and lasting effects on the more unstable nerve centres of the child.

But in addition to the theories just mentioned there is another, due apparently to the late Dr. Kirkes, which makes chorea due to embolism of the minute vessels of the brain (corpora striata), the emboli taking origin from the previously inflamed valves of the heart.

And it seems to me that a slight modification of this theory, making the embolic particles originate, not in the valves of the heart, but in what I have called a snowstorm of colloid uric acid in the blood, some of the particles collecting and forming here and there more or less permanent obstructions in the minute vessels of the brain. Such a condition would help us to explain, not only the occasional morbid appearances found after death, but would more or less completely account for several points with regard to chorea which remain inexplicable on other theories.

This condition of the blood, which I have called collæmia, is, to my mind, the cause of the general obstruction to circulation and the consequent high blood-pressure which uric acid produces (see chapter 5).

As a rule the obstruction is partial and temporary only; the colloid particles pass through the capillaries, though slowly and with difficulty, and then being carried by the veins to the deeper and warmer parts of the body are, as a rule, re-dissolved.

But under *slightly altered conditions* several of these snow flakes may adhere together, and form a mass capable of completely obstructing a capillary or set of capillaries, and so alter, for a longer or shorter time, the function and even the structure of the surrounding portions of the brain.

I have already for some years been suggesting that embolism or thrombosis, thus originating in colloid particles of uric acid in the blood-stream, may account for the well-known relationship between such troubles and gout (see also my remarks on thrombosis in chapter xii., p. 417).

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I have also pointed out that causation by the obstructing influence of colloid uric acid in the blood will account for one feature of Raynaud's disease which is otherwise inexplicable, namely, its limitation to surfaces and extremities, *i.e.*, to exposed portions of the body, and the effects of local cold in producing Raynaud's disease, as by washing the hands in cold water, are well known. I have already mentioned, also, the probable relation of collæmia to cold acids, &c.

And now we come in sight of one of the altered conditions which may make the difference between mere temporary and more permanent obstruction of capillaries by collæmia, and it will be found also to give us an explanation of the well-known large preponderance of chorea cases in girls, which seems to be from two or three to one.

I have already given this same condition in chapter xi. as the cause of the increased frequency of Raynaud's disease in girls; and I have there suggested that as girls differ from boys chiefly in having a less well developed muscular system, they will have also, probably, a less powerful heart; and this may just make the difference between the slight temporary obstruction of their capillaries by collæmia, which produces cold hands, and the more severe and permanent obstruction which brings about actual Raynaud's disease; and we can see that the washing in cold water will act just as cold in the test tube (chapter v.), by determining or increasing the precipitation of the colloid, and make the difference between a few flakes of snow and a blinding storm.

Now, obviously, exactly the same explanation will apply to the preponderance of chorea in girls if it is due to collæmic embolism, for a little weakness of the heart muscle may just suffice to make the difference between such slight and temporary obstruction of capillaries as causes general high blood-pressure, and the more permanent or lasting obstruction which is the possible cause of chorea.

The same fact may also serve to explain the great value of rest in bed, which will relieve the heart of much work; and arsenic not only clears the blood of uric acid, but, as is well known in countries where it is eaten, strengthens the heart and the muscles in general.

Then again the endocarditis, which may or may not accompany chorea, is probably one of the results of the high blood-pressure which, as has been already explained in this chapter, if it strains and irritates the fibrous tissues of the valves may lead to the precipitation of urates upon them, and so to this further irritation and the origination of endocarditis.

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Here, again, the presence or absence of endocarditis may depend upon whether the heart is rested or worked at the beginning of the disease.

Again, such a causation will enable us to understand completely the relationship of chorea to shock and to fatigue.

Almost every shock, mental or bodily (and they are generally both), suffices, if at all severe, to suspend digestion, to lower the hourly excretion of urea and of acid in the urine, and so to increase to a corresponding extent the alkalinity of the blood; and thus, especially in children, to flood it with uric acid; hence shock often suffices to bring on megrim, epilepsy, or mental depression in those who suffer from these.

Graves' disease, which I have already suggested (p. 124), may be due to unrelieved high blood-pressure, may also originate in a similar mental shock (see Sir W. Broadbent, "The Pulse," p. 90).

The effect of fatigue in producing uricacidæmia in those who have large stores of uric acid, has already been treated of at great length in chapter viii., and its bearing on the collæmic causation of chorea is obvious.

Some interesting suggestions are made by Dr. Churton (*British Medical Journal*, 1896, vol. ii., p. 715) bearing on these points, one of which is that chorea may be due to direct irritation of the nervous system by shock or excitement determining the toxin to that system, just as a wetting determines arthritis of the upper or lower extremities, as the case may be. And further on he says: "But arthritis is never the first result of fright, and chorea is never the first result of chill." Exactly so, for fright causes depression and uricacidæmia, which is the opposite condition to arthritis; and chill causes a fall in the alkalinity of the blood and clears the uric acid out of it into the joints producing arthritis, which is the opposite condition of uricacidæmia, collæmia, and chorea.

It is only fair to say that Dr. Churton adds to the above quoted lines "unless fear or brain excitement accompanies the chill"; but I am concerned with the rule and not with the exception, and the rule is that fear causes uricacidæmia and depression, and chill clears the blood of uric acid either locally or generally, and may thus produce arthritis, or inflammation of any fibrous tissues.

I will now shortly mention in illustration of some of these points a case recently under my care. It is that of a girl, age 16, admitted into the Metropolitan Hospital with her third attack of chorea on March 14, 1897. There is no sign of endocarditis, either recent or of old standing, so that this cause is probably absent.

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Her mother is a sufferer from megrim, and one of her mother's sisters had chorea in childhood.

The patient herself suffers from such headache (uric acid headache) from time to time, and had several bad attacks in rather quick succession just before this last attack of chorea came on.

The determining cause of this last attack seems to have been an injury resulting in a severe cut on the thumb of the right hand, which formed a rather ugly wound at the time of admission.

Here then we have a shock as the determining cause, and we have this supervening upon the passage of a considerable amount of uric acid through the blood, as shown by the frequently recurring headaches.

On admission she was also noted as being extremely anæmic, and as having suffered more or less from this for some time. She also presented all the signs of debility and exhaustion.

But we know much more than this—we know why she was anæmic, why she had uricacidæmia, collæmia, and frequent headaches, for she was in service in what is known as a "hard place," and this would undoubtedly produce fatigue and uricacidæmia; and we know also that uricacidæmia at her age, three years after the year of greatest growth (see chapter xii. and fig. 51), would of necessity be severe, and this would, as is common in girls of her age, produce chlorosis; further, the collæmia would be signalised by exactly what we find in her history—severe and rather frequently recurring headaches. It may not be without interest to remark in passing that epilepsy very frequently begins in girls just at the age of this patient, and no doubt it does so as the result of exactly the same causes as those that rendered her headaches both more frequent and severe; and epilepsy also is another disease closely associated with collæmia, and may apparently be originated by a fright or shock. Then the progressive fatigue, collæmia, and anæmia would be certain to react on the nutrition of the muscles and the heart and weaken them.

This then was her condition when, on March 9, a china basin fell on her hand and cut it severely.

This, no doubt, caused a considerable shock, which intensified the uricacidæmia and collæmia by further upsetting nutrition. The collæmia would have raised the blood pressure and caused headache, but the heart had now failed before its accumulating misfortunes to such an extent that it was no longer able to keep up the blood pressure; and so, as she herself tells us, there was no headache, but the choreic movements soon began, for there was collæmia and

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collæmic blocking of the capillaries of the brain was favoured by the very weakness of the heart which rendered headache impossible (see remarks on antipyrin on p. 206).

The pulse on admission five days later was 144, with a temperature a little above 99, but the very violent movements may quite account for this and the signs of exhaustion which were also most marked.

She was given injections of morphine to quiet her on the first day, and then put on a small dose of arsenic; and in two or three days she was much quieter and even able to speak a few words.

The movements continued, but less violently, for many weeks, but by the end of April they were almost gone, and she was allowed to be up for a little; she was continuing the arsenic, and gaining weight.

She was still, however, decidedly anæmic, say blood decimal by sight ·35 to ·4, and had a quick pulse.

Her previous attacks of chorea, first at 10 years old and second at 12 years old, were much less severe than the third, and this is interesting, as she would probably have less uric acid available before her year of greatest growth than after it; and I cannot help thinking that if she had been on a uric acid free diet from the date of her second attack she would now have escaped the collæmia, anæmia, headaches, and chorea.

For an interesting case in which chorea apparently followed on depression, hysteria, and excessive irritability, these being all signs of collæmia and coming during menstruation, its frequent cause, and in which embolism and thrombosis of certain vessels were found after death, see *Brain*, July, 1889, p. 157. And for a case in which chorea came on as rheumatic fever left off, that is, when there was almost certainly collæmia, see *British Medical Journal*, 1894, vol. ii., p. 1,227. But chorea follows other acute diseases besides rheumatic fever, for every acute disease in a child is followed by post febrile collæmia (see also article in *Progrès Medicale*, April, 1888, p. 301).

The chief point in the treatment of all uratic arthritis, whether it presents the clinical picture of gout, rheumatism or rheumatoid arthritis, is the removal of the urate, and the more acute the symptoms the more important is this indication.

When, however, all the conditions are chronic, when there is little or no temperature, and the pain is remarkable rather for its extent than its intensity, and when drugs like iron can be taken without markedly increasing the pain, the removal of the urate has already probably to a large extent been effected by nature, and

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the indications are then rather to treat the damaged structures it leaves behind.

The first indication is met by salicylates, or, if there are good reasons for not using them, then by alkalies.

The salicylates must be given in a sufficient dose, because, other things being equal, the amount of urate eliminated depends on the amount of salicylate in the blood to combine with it. I have seen gr. x. of salicylate of soda given three times a day in acute rheumatism without the smallest effect, when gr. xx. every two, three, or four hours promptly relieved.

Salicylate of ammonium is by some considered to be less nauseating than the sodium salt, and for the reasons previously mentioned it has probably some advantages over it as regards the elimination of uric acid, especially in subacute or chronic conditions.

There are but few reasons for not giving a good dose, the head symptoms they produce are generally trivial, and in albuminuria and Bright's disease there is but small evidence that they really increase the albumen.

If they do cause a little depression, what is that to the depression of a prolonged attack of acute rheumatism? And it seems that at least a part of the depression they have been credited with is really due to impurities which we are gradually learning to eliminate (see an interesting article by Dr. Lees, *Lancet*, 1893, vol. ii., p. 190).

In cases where salicylates by mouth cause nausea or vomiting, which may either completely prevent their being taken, or, if not, upset a large part of their action by altering the alkalinity of the blood, the local use of salicylate of methyl[1] should not be forgotten, as this may affect the local conditions more quickly from being applied locally, and there being thus a smaller dose in the blood in general, the general symptoms produced by it will be less troublesome. It is, however, quite possible to give too large a dose of salicylate by the skin if it is applied too freely or over too large a surface. Salicylate of methyl is often also a useful addition to a moderate dose by mouth, as, for instance, when one or two joints hang back from the general improvement, but it is not desired to increase the dose by mouth; and there are a whole host of minor gouty and rheumatic troubles in which its local application quickly suffices to cure. In my experience moderately extensive local application twice a day has sufficed to cure acute rheumatism.

[1] As advised by Lannois and Linossier, *Méd. Mod.*, August 19, 1896.

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The second indication requires nourishing food, perhaps wine, cod-liver oil and alteratives such as the iodides, various tonics, sulphate waters, compounds of sulphur, &c., mentioned before; these may act partly by improving the circulation through the damaged structures, but also, as suggested above, partly by keeping the blood moderately clear of uric acid, so that there is none to be precipitated upon the joints (fig. 63, 11.0 p.m.) and increase their irritation. Then blisters, massage and electricity may obviously affect local nutrition, and so the uric acid and its effects upon these.

With regard to massage I think we must bear in mind that by improving the circulation through the injured tissues and flooding them both with fresh blood and fresh alkaline serum it may really do a great deal in removing the irritating urates.

While these urates are present or are liable to recurrent precipitation on the damaged structures with the daily, almost hourly, fluctuations in the alkalinity of the blood, we may have to deal with a progressive condition of irritation, leading to ever increased fibrosis and stiffening, and that whether the original condition was uratic or traumatic; for in those whose fluids are full of urates every traumatism of fibrous tissue is sure to be irritated by their presence and recurrent precipitation so long as the seat of injury is less alkaline than the blood and tissue fluids of the body.

Now the effect of massage on an injured fibrous tissue is to flood it with fresh blood and to bathe it through and through with fresh serum as shown perhaps by considerable increase of swelling after the massage.

The swelling, however, goes down again, and the serum is taken back again into the circulation, and not only takes with it some of the urate that caused the irritation, but also some of the acid salts that rendered the fibrous tissue a seat for urate accumulation; hence it comes about that repeated massage every two or three days for a couple of weeks may not only remove the urates which are the cause of the irritation in the fibrous tissue, but may render it as alkaline as the blood and tissue fluids in general, and therefore no longer a seat for chronic and recurrent retention of urates.

Here we see possibly another reason for the rapid and satisfactory repair of wounds and injuries in those nations, as the Turks, who live on an almost uric acid free diet; they have not only, as already pointed out, a greatly improved circulation owing to absence of collæmia and a better supply of alkali for their damaged fibrous structures, but they have also far less uric acid to be precipitated upon these structures and keep up the irritation. Hence these

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people get well simply and naturally without the opium and without the subsequent massage that are so often required by the urate laden meat eater.

Do we not here see also at least a partial explanation of the good results produced by so-called "bone setters," who break down and subject to massage the fibrous tissues round an old traumatism?

Then there is one indication which is common to both conditions, namely, to keep as low as possible both the introduction and the formation of uric acid, and of this I shall have to say a good deal in the following chapter.

But if there is anything in what I have suggested as to the causation of those diseases, if there is any truth in the observations of M. Bouchard which I have quoted, we ought to be able to prevent these troubles, and I, for one, believe that we can.

And a hint of something of this kind is intended, I think, to be conveyed in the following passage from the very interesting address on medicine delivered by Dr. Drummond at Newcastle (see *British Medical Journal*, 1893, vol. ii., p. 300), where he is reported as saying: "Would a substantial reduction in the number of chronic heart cases as the result of the recognition of the fact that many are due to curable and preventable causes which an early and successful treatment might reasonably be expected to subdue, be a dream too visionary for us to indulge in? I think not; but assuredly until we fully appreciate the causes a dream it will remain."

I believe that if the children of rheumatic or gouty families can be placed early in life on a diet which reduces as far as possible the uric acid directly introduced, and at the same time reduces so far as is compatible with healthy nutrition, the formation of uric acid in their bodies, such children, in spite of their inheritance, may never suffer from either disease. I shall never lose an opportunity of doing this, and would strongly urge others to do the same, for this change of diet which promises so much, can as I shall endeavour to show in the next chapter, be effected without any damage or risk.

I further believe that those who have suffered from these diseases, whether they have damage in joints, endocardium or other fibrous structures, can to a very large extent prevent their damage going further, by a similar change of diet continued for the rest of their lives. I have been acting on this principle for several years, and have, I think, every reason to be gratified with the results, some of which I have mentioned.

Climate again has great importance in the treatment of chronic arthritis, for a moist relaxing climate keeps the blood alkalinity

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high; it is consequently but rarely free from uric acid, and every fluctuation of acidity causes fresh or increased joint irritation; on the other hand, a dry bracing climate keeps the alkalinity of the blood low, the patient feels better and stronger, the blood is relatively free from uric acid, and the joints have a little rest and time for repair.

See also the remarks in the previous chapter on the effects of climate on gout; and of rheumatism Dr. Solly says (previous reference, p. 180): "Articular rheumatism is more common in a cold climate than in a warm one, and in a damp than a dry atmosphere"; and the effects of these factors on the skin and the excretion of uric acid I have already gone into.

The treatment of morbus cordis, so far as it is due to valve or peri-cardial lesion, has hitherto comprised little beyond the use of tonics and stimulants, but it is evident from the case of A. S. mentioned above, that we must be very careful not to use these tonics and stimulants too soon, or while there is any heat or irritation remaining about the valve, or we shall only make it blaze up again, and, precipitating more urate upon it, make matters worse.

While valve lesions are recent, I think we can hardly do much better than follow the treatment suggested by Dr. R. Caton (*Lancet*, 1895, vol. ii., p. 399), which consists in giving gr. x. of an iodide three times a day, in addition to salicylates, and placing repeated small blisters on the chest wall over the damaged valves.

The salicylates effect the elimination of uric acid, while the iodides keep them from combining with alkalies and raising the blood pressure, which would increase the work the heart has to do.

It seems to me that we must rest the valves as much as possible and not expose them to any strain that can be avoided, and that we must do all we can to restore their normal alkalinity; and, lastly, I think we must keep on with salicylates for a good long time, I should be inclined to say for several months at least, to protect them from the evil effects of exposure to cold or the accidental use of acids or other things that affect the solubility of uric acid, and also to make as sure as possible of sweeping out every atom of urate from the affected fibrous tissues (see previous remarks, especially those in chapters xv. and ix.).

And last, but not least, diet should be carefully attended to, so that there should be as little uric acid as possible in the blood, and thus the valves might be kept free from either the strain of high blood pressure or the irritation of local precipitation.

With regard to the morbus cordis of later life, which is specially

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associated with high blood pressure, we must apply the principles laid down in chapter v. for the relief of this condition, and generally speaking we shall do far more good by freeing the capillaries, lowering the blood pressure, and thus relieving the heart of unnecessary work (as pointed out by Sir W. Broadbent, "The Pulse," p. 262), than by stimulating it with alcohol, digitalis or nux vomica; these may be useful enough when the capillaries are free, but the first thing to do in the morbis cordis of later life is to be sure that they are free.

And when the drugs have acted well and the patient is free from immediate danger of syncope, heart disease, angina or whatever result the high blood pressure was producing, we must not forget the diet treatment of high blood pressure, which will do more to prevent future attacks than any drugs (see also "Notes on the Treatment of Morbus Cordis by iodides and other drugs which lower the Blood Pressure," *Therapeutic Gazette*, September, 1895).

And though it is difficult to say anything definite about chronic morbus cordis I am decidedly of opinion that I have several times seen very marked improvement in the condition of the heart and circulation as the result of permanent alteration of diet habits; and this is not very surprising when we remember the important effects thus produced in keeping the blood clear of uric acid and lowering the blood pressure. And some experiences of these effects of diet I have recently shared with Dr. Gayford, of Fleet Street, E.C., have inclined me to give a much more favourable prognosis of the morbus cordis of rheumatism if it can be treated over a long period by a uric acid free diet.

We must bear in mind also the active metabolism in children, and the fact that they form much more urea and uric acid per pound than adults, and this makes it all the more important to do nothing to stimulate nitrogenous metabolism, and not to introduce a single grain of uric acid that is not necessary. It is not, however, uncommon to find that mothers of such children are in the habit of dosing them with beef-tea because they do not care for meat, and thus Nature's effort to protect them is nullified.

The treatment of chronic arthritis, whether called gout, rheumatism, or rheumatoid, associated with considerable debility, often presents difficulties which necessitate its special consideration. Let us for a moment take a fresh survey of our position; we are dealing with an arthritis which originated in the irritation of uric acid, which, if acute and febrile at first, is now chronic with little or no temperature, and associated with more or less marked debility

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and failure of nutrition; it occurs in the body of a person who, owing to habits of diet extending over many years, has accumulated much uric acid in various tissues and organs, and the slow solution of this, and its passage through the blood day after day, which always takes place in conditions of debility, probably keeps the irritation of the affected fibrous tissues smouldering on, as we saw in the case of the endocarditis to which fig. 60 refers.

Now, the first indication is to get clear of the urate accumulation as soon as possible, but as there is debility and little or no fever, salicylates will as we know not act well, and we must therefore do what we can to counteract the debility, so as to get their best action.

To this end I give a liberal diet, containing a full physiological allowance of nitrogen, but as little uric acid or xanthin as possible; that is to say, I substitute as far as circumstances permit, milk, cheese, and pulses for animal flesh, but am careful not to endanger nutrition, and I always give animal food freely if the other unaccustomed foods are not well taken; some wine should also be taken two or three times a day, as its acids are valuable, and it may aid digestion. If by these means we can stimulate and improve nutrition, the patient may then get into a favourable condition for the best action of salicylates, and they may be given either with or after a course of tonics, according to circumstances.

Where the debility is very great, the best plan may be to give the above diet along with tonics and drugs of the iodide class, which clear the blood of uric acid and allow the joints and the metabolism generally a little rest and time to recover. When pains are less and nutrition better, associate salicylates with the tonics or give them in sequence to them, and let the salicylates be taken every alternate week for several months (4 to 10 or 12 or more), so as to get the action referred to on p. 520, and when most of the urate accumulations have thus been cleared out (for salicylates will eliminate both the urates deposited and those introduced in the food), leave them off, together with the animal food and the wine, and begin a really uric acid free diet.

In this way we may hope to get free of urates and to keep free, and thus to place the joints in the most favourable position for complete and lasting recovery.

Among tonics which are useful in the above conditions of debility are the iodides, as in the old-fashioned mixture with tinct. cinchonæ co. with or without the addition of nux vomica, or some lithia to further aid the iodide in clearing the blood of uric acid.

Then calcium salts and various acid resins may be useful, and

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in the following are represented I think most of the important ingredients of a proprietary medicine which has a considerable reputation for curing chronic gout and rheumatism and acting as a tonic. Tinct. cannabis indicæ, ℥vi.-xii.; liq. calcii. chloridi, ℥xv.-xx.; tinct. chiratæ, ʒss; inf. gent. co. ad. ʒi. This is not a pleasant mixture, but it is a powerful tonic and clearer of uric acid out of the blood (see pp. 53 and 164); it may be taken freely diluted once a day at first, and then more often, and generally between meals or about one hour before them.

Lastly, we must not forget arsenic, the drug which is so much used in so-called rheumatoid arthritis, which, as we have seen, is often nothing but gout with extensive joint changes, for like the above it is a tonic, and as we know, probably also clears the blood of uric acid.

Any of these things may be continued with advantage for months or years, and then be either associated with or followed by salicylates, and these by a uric acid free diet.

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CHAPTER XVII.

Treatment.

After all "the proof of the pudding is in the eating," or rather, in this case, the proof of the poisonous nature of flesh and tea lies in the effects of refraining from eating and drinking them, and the best possible tests of the truth and stability of the above considerations are the results that can be obtained by applying them in practice. It matters little to those who suffer whether the poison in the blood is uric acid or xanthin; but it matters everything to them if by altering their diet and getting their nitrogen from one source rather than from another, they can free their blood of the poison and themselves of the diseases it produces.

Many volumes of theory did not suffice to prevent one of my headaches, but once I found out that they were due to poisoning by meat and tea prevention became both certain and simple, and relapse is now a mathematical certainty if these poisons are again taken in any form.

The diseases treated of in the first fourteen chapters are more or less directly due to excess of uric acid in the blood, those in the fifteenth and sixteenth are due to this excess of uric acid being driven out of the blood into certain fibrous tissues. The diet treatment of these diseases is the keeping the body and blood free from an excess of uric acid, and we have now to consider the way in which this can be done.

Now, uric acid is met with in excess in the body and blood chiefly, as we have seen, from three causes: (1) that it has been introduced in excess by the consumption of articles of food such as meat, eggs, fish, tea, coffee, cocoa or guarana, which contain it or other members of the xanthin group equivalent to it; or (2) because so much nitrogen is taken that the uric acid formed out of it in the relation to urea of about 1—35 is, owing to the high acidity which the salts and other products of nitrogenous metabolism produce, not all excreted, and a store is gradually formed in the body to the extent possibly of from 52 to 400 grains in a year; (3) the high acidity which

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results from the taking of much animal food prevents the excretion of the uric acid introduced with this animal food, as well as that which is formed out of its nitrogen along with a certain quantity of urea. In a word, animal food increases the introduction and formation of uric acid and at the same time prevents its elimination, and the alkaloids of tea, coffee or cocoa and certain similar vegetable products act in exactly the same way.

Speaking of guarana, reminds me that it is probably by its nitrogenous or xanthin elements that it cures sick headache (uric acid headache), because strange as it may seem at first sight, a dose of uric acid itself will cure a uric acid headache, and as we have seen in chapter iii., the first effect of a dose of uric acid, and probably also of ammonia and nitrogen in other forms, is to raise the acidity and clear the blood of uric acid; and I remember years ago, before I began to study medicine, pointing to a big plate of meat in front of me, and saying, "My headache will be all right when I have eaten that." I now know that the nitrogen and salts so introduced raised the acidity of the urine, reduced the alkalinity of the blood, and cleared it of the uric acid that was causing my pain. But I would earnestly warn any fellow sufferer against treating his trouble in this way, for I believe it to be a most dangerous course; the uric acid thus cleared out of my blood was not cleared out of my body, and in addition more was introduced, and for years afterwards I suffered from most terrible headaches, while the urates thus stored up were passing through the blood, and I believe that damage was then done to my heart, vessels, and other structures, which no subsequent change of diet has sufficed to wipe out.

I would say, further, do not under any circumstances resort to caffeine or guarana for relief; they are practically uric acid, and present relief is obtained at the price of future suffering, and I have seen several cases in which the employment of these substances for some considerable time for the relief of headaches, &c., has been followed by very deplorable consequences.

With regard to diet, we can give the main point in very few words, for we have seen that as flesh diet increases the introduction of uric acid, it increases the formation of uric acid, and its salts diminish the excretion and elimination of uric acid. A milk and vegetable diet, provided that no excess of albumens is taken, introduces less uric acid, causes the formation of less uric acid (because urea is not unnecessarily high), and its salts promote the free elimination of all uric acid that is introduced into or formed in the body. Thus we see (p. 11), that I excrete now 11·9 grs. of uric acid,

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of which 10 grs. are formed in the body, and 1·9 grs. are introduced ready formed, while a fraction of a grain is accounted for by the excretion of urates previously stored in my body. With this low formation and introduction of urates I have but rarely any excess in my blood, and consequently suffer little or not at all from headache and other signs of such excess.

In former years on ordinary diet I used to excrete 500 to 600 grs. of urea, and in the above proportions I must have formed 14-17 grs. of uric acid and introduced from 3-4 grs. ready formed in my food. It is easy then to see why I often had an excess of urates in my blood, and frequently suffered from the effects of such excess, namely, high blood pressure, headache and mental depression. Further, I believe that the section of mankind that lives to eat may possibly introduce as much as 2 grs. of uric acid with each meal, or 6-8 grs. in a day or more, and sooner or later will suffer in proportion.

We can now quite understand why in Persia, where only the rich eat meat, gout has come to be known as the rich man's disease (see *Proceedings of the Royal Medical and Chirurgical Society*, third series, vol. v., p. 46, where this interesting fact is contributed to the discussion on my paper on the iodides by the physician to the Shah), and we have already seen on page 414, that the children of the rich are in this country specially liable to anæmia, no doubt due to excess of meat in their food, and in chapter xvi. we have seen that M. Bouchard considers that children thus overfed are liable to many troubles, including migraine and acute rheumatism.

We have, then, two things to do to attain our object: we must cut off all food which contains much uric acid, and which is not absolutely necessary; and we must not take more nitrogen than is necessary to keep our urea at the physiological level of 3·5 grs. per pound of body weight per day.

With regard to cutting off we may, I think, at once forbid tea, coffee and cocoa, or permit them only in the smallest possible quantities as flavourings. We may cut off at once such animal food as contains much uric acid, and give only so much of the less harmful kinds as is necessary for nutrition.

This raises at once two questions:—

(1) What animal foods contain much uric acid?

(2) How much animal food is necessary for nutrition?

I can answer neither question completely, but I must nevertheless attempt to do what I can, and hope that further knowledge, when we attain it, will not show that I have been very far wrong.

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There can be very little doubt after what I have said, that the best answer to our question is to be obtained by the physiological test which I have used in the case of meat (see p. 95, and *Journal of Physiology*, vol. xv., p. 168).

That is to say, when a person is on a practically constant diet, and is watching his uric acid and urea excretion from day to day, if the taking of a known quantity of some substance, such as fish or meat, always without exception, increases the excretion of uric acid out of proportion to urea, such substance probably contains an excess of uric acid which it introduces into the blood, and should consequently be as far as possible avoided by those who suffer from uricacidæmia.

Such a physiological test is much more valuable than any mere estimation of the xanthins contained in meat can possibly be, for what we want to know is the effect of these substances on the living human body, and in so far as meat eating produced my headaches, it was no doubt, as we can now understand, the xanthins it contained, which probably by conversion into uric acid raised the blood pressure and increased the excretion of uric acid in the urine.

In eggs, for instance, I have been unable to find any uric acid or other members of the xanthin group, such as I have found in meat, and yet their steady and graduated administration invariably brings about a large rise in the excretion of uric acid, and all the evil effects of its passage through the blood, so that I have had to exclude them entirely from my diet.

We must, therefore, take the following table as at best but a very rough guide to the amount of uric acid or xanthin in any food, and the ultimate appeal must always be to the effects of administration on the excretion of uric acid from day to day (see also p. 8 and fig. 64).

Substance.	Uric Acid and Xanthins. per cent.	Grains per lb.
Lamb (cold roast leg)	·050	3·5
Soup (made from bones)	·0068	0·48
„ (made from meat)	·0202	1·4
Hospital beef-tea	·0980	7·0
Saddle of mutton	·020	1·4
Mutton (cold roast leg)	·016	1·1
Veal (cutlet)	·049	3·5
Beef (cold sirloin)	·016	1·1
Kidney of sheep	·049	3·5
Liver „ „	·091	6·5
Fowl (breast)	·024	1·7
Rabbit	·015	1·0

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Substance.	Uric Acid and Xanthins. per cent.	Grains per lb.
Mackerel	·032 ..	2·2
,, (boiled only ½ of an hour) ..	·015 ..	1·0
Plaice	·0039 ..	0·2
Herring (fresh)	·0040 ..	0·2
,, (Loch Fyne, kippered)	·0900 ..	6·4
,, (bloater)	·031 ..	2·2
[1] Beef-steak (treated raw)	·019 ..	1·3
[1] Meat-juice	·697 ..	49·7
[1] Meat extract	·883 ..	63·0
Tea	2·5 ..	175·0
Coffee	1·0 ..	70·0
Cocoa	·84 ..	59·0

The tissues were extracted as cooked and ready for eating, except as mentioned, and I give uric acid in grains per pound as well as in per cents., as it has been suggested to me by Dr. Rushton Parker that this would make the table more useful.

We see from this that young meat (lamb and veal) contains more than old (beef and mutton), and that, as we should expect, soup made from meat contains considerably more than soup made from bones. We see also that the kidney and liver of sheep contain considerably more than their muscles, just as is the case in man, and some kinds of fish appear to contain a considerable quantity even more than meat, and any increase in the fish taken has certainly appeared to me to markedly increase the amount of uric acid passing through the blood.

The fact that hospital beef-tea contains so much uric acid is interesting, and a pint of this beef-tea, I am informed, was made by cooking 1 lb. of meat for eight hours.

It appears, then, that this process extracts about five times as much as I have obtained from similar muscular tissue, but then I only boiled it for half an hour (see chapter xviii.). This seems to render it probable that I have only extracted from the tissues in the above table from a-quarter to half of the uric acid they really contain; getting relatively more from the younger or softer tissues which broke up more easily, and relatively less from the older and tougher tissues.

As regards the animal foods, their infusions and extracts, the figures given represent uric acid plus other members of the xanthin group, and tea, coffee, and cocoa contain xanthin compounds not

[1] These are from p. 73, placed here for comparison.

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uric acid; but as I have pointed out in the early chapters of the book, these may, for all pathological and physiological purposes, be regarded as one and the same substance, producing throughout the body and its tissues the same effects.

Then I find that a single supper or dinner of soup, fish, and meat appears to increase the urate excretion of the following three or four days by about 4 to 6 grs.; but the animal food taken at such a dinner, including soup and meat extracts, probably does not exceed the equivalent of three-quarters of a pound of meat, so that the results of digestion appear to correspond fairly well with those of long cooking in the case of the above beef-tea.

It needs also but a very simple calculation from the figures in the above table to show that tea is by no means the harmless substance it has been supposed to be, and that in place of causing a little dyspepsia by tanning the gastric mucous membranes, it may really bring about, in the course of a year, the introduction of a huge quantity of uric acid, and thus account for some of the most serious effects of uricacidæmia or arthritis, of which we had probably one instance in chapter vii., p. 238.

I may mention, while speaking of tea, some figures kindly sent me by Dr. C. E. Lockwood, of New York, as obtained by a friend of his, Dr. W. J. Morton, while experimenting on himself with tea. He took from 4 to 8 drachms of green tea infused in a pint of water, and continued it for seven days, and as a result uric acid rose from 5 grs. up to 8, 10, 11, and 13 grs., while urea fell steadily from 591 grs. to 422 grs. in the same time, this fall of urea probably illustrating the depressing effects on metabolism of excess of xanthin or uric acid in the blood.

And now for our second question—How much animal food is necessary for nutrition.

I have had in my own experimental work the most absolute proof, if further proof is needed, that a sufficient supply of nitrogen is the prime necessity of nutrition.

For before I became aware that the uric acid which poisoned me was being poured in day after day ready formed in flesh foods, tea, coffee, &c., I believed that the only way to reduce uric acid was to reduce total nitrogen, and this I proceeded to do with the unfortunate result of reducing myself to a condition of extreme debility and asthenia.

But when I found out in 1893 that all uric acid and xanthin swallowed got into the blood and eventually into the urine, I was at once able to see that I could take as much nitrogen as was neces-

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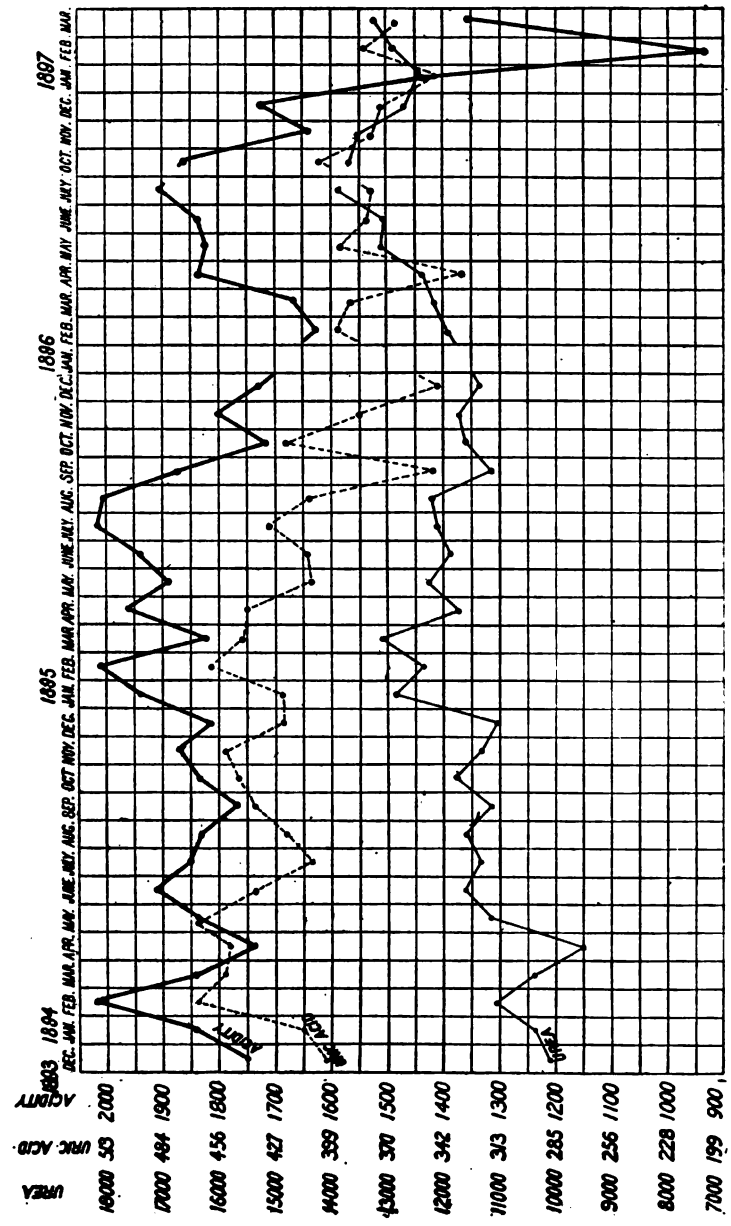

FIG. 64.—URIC ACID, UREA AND ACIDITY EXCRETIONS MONTH TO MONTH, SHOWING EFFECTS OF DIET OVER YEARS

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sary for nutrition as long as I avoided substances which contained much uric acid or xanthin.

I will now show in fig. 64 an epitome of my results during the last four years, each dot in the curves there given corresponding to a month's excretion.

The figure begins with December, 1893, where we see urea is very low, at 10,000 grs. in the month or 322 grs. a day, which for 125 lbs. of body weight is only about 2·6 grs. per pound per day; but uric acid is high, 12·8 grs. per day, giving a relation of uric acid to urea of 1 to 25.

From this onward we see a steady rise of urea till in February, 1895, it has reached about 387 grs. a day, and in June, 1896, to about 419 grs. a day. And uric acid, which was above 14·7 grs. several times in 1896, and above 13·7 in 1895, falls towards the end of this year (1895) to 11·9, and has remained about this level ever since, its relation to urea in the early part of 1897 being very close to the supposed level of formation, 1 to 35.

So that at the present time the uric acid excreted in a year is nearly 500 grs. less than in 1894, and urea is nearly 30,000 grs. a year more.

The great fall in uric acid is entirely due to the gradual elimination from my diet of substances containing it or its xanthin relatives. Thus up to the early part of 1894 I was taking both fish and eggs, in 1895 I took fish perhaps once a day, at the end of 1895 I took neither fish nor eggs, and in the latter part of this year and the whole of 1896 I gradually eliminated from my diet all articles that contained even the smallest quantities of egg, such as puddings of various kinds, and cakes, as I got very distinct evidence that these when taken every day very decidedly increased the excretion of uric acid.

The curves tell their own tale and show that I am now practically free from uric acid, and that the small output of this substance is not due to its small excretion or retention owing to rising acidity and urea, for in February, 1897, I took a large amount of alkali and greatly reduced the acidity of the urine, and yet the resulting rise of uric acid was very small indeed, showing that there were practically no stores in the body available for solution.

I would point out that with this great fall of uric acid my blood decimal has gone up since 1894 fully 10%; that my pulse is now never so slow or my blood pressure so high as it used to be, that headache and mental depression are steadily and completely absent, while nutrition, strength, and power of endurance are better now than at any time during the last 15 years.

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It may be said that the improvement in the blood decimal is due to the rise of urea, and this is no doubt correct to some extent, for the nutrition of this circulating tissue must have improved along with the rest; but this will not explain the fact that the blood decimal fluctuates with the hourly and daily fluctuations in the excretion of uric acid, and that both in myself and others the swallowing of uric acid or any of its xanthin relatives will promptly bring it down without affecting urea at all.

This figure, therefore, shows that the excess of uric acid and the diseases it produces are almost entirely matters of introduction, that no reduction of urea compatible with life will bring down uric acid so long as introduction is continued; but on the other hand so long as uric acid is not introduced urea may be kept up at any height required by physiology to furnish the greatest amount of force the body is capable of producing; that with sufficient urea and in the absence of all excess of uric acid it can furnish force for nutrition and strength and power of endurance to an extent which is very greatly in excess of anything that can be done when fed on animal flesh and vegetable alkaloids.

My experience, therefore, leads me to answer the question of the quantity of animal food necessary for nutrition as follows:—

No animal food at all is necessary, for the whole of the required nitrogen can be got from the vegetable kingdom, but as milk and cheese appear to have no power of increasing the excretion of uric acid, they may be used along with the vegetable foods.

As to the quantity of nitrogenous food required, my experience leads me to believe that the allowance given in most works on physiology of 3·5 grs. of urea per pound of body weight per day, is very close to the mark for a healthy and active adult man.

Children may require nearly three or four times as much, as they have to grow as well as to keep up nutrition; sedentary adults require less, and those who are old as well as sedentary much less.

Thus, for myself, I believe that somewhere between 3 and 3½ grs. per pound per day is the best amount of urea, near the higher limit when I am taking a considerable amount of exercise regularly, and near the lower when I am very sedentary, as in bad weather in winter.

Then as urea multiplied by three equals roughly the albumen required to produce it; if the weight is known it is easy to calculate approximately the quantities of the various food substances that will have to be taken by any given person.

Such a calculation should, however, only be used as a rough

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guide; as appetite on the one hand, and nutrition, strength and power of endurance on the other, are the most certain indications of the necessary quantity and quality.

The rule then for an active adult is—find the body weight in pounds; if there is much adipose tissue deduct it, *i.e.*, take the weight of the individual before he began to get stout, multiply by 3·5 and the resultant by 3 and you will have the amount of albumen in grains that he will have to consume each day.

Thus a man of 140 lbs. × 3·5 = 490 × 3 = 1,470 grs., the amount of albumen to be taken by him each day.

He has got to leave out all meat, fish, fowl, game and eggs, which contain say 20 to 25% of albumen and to replace them by—

Milk	containing	3—4%	of albumen.
Cheese	,,	33%	,, ,,
Pulses	,,	22%	,, ,,
Bread	,,	8%	,, ,,
Oatmeal and other cereal foods	,,	5—12%	,, ,,

He may also have garden vegetables, but these often contain mere fractions of a per cent of albumen, or garden fruit containing from ·5 up to 1·0, 2·0, or 3·0% of albumen only.

Practically, then, he will have to replace his flesh foods by milk, cheese, pulses, bread and corn foods, and regard garden vegetables and fruits as palatable but not very nourishing additions to them.

Obviously most of our fruits contain so much water that huge quantities would have to be taken to get the necessary albumen, but this does not apply to the denser fruits or to those which have been dried or compressed, which may contain as much albumen as the cereal foods or bread.

So our man of 140 lbs. would have to take, in order to get his 1,470 grs. of albumen—

10 oz. bread	(= 8% of albumen)	—344	grs. of albumen.
[1]2 oz. oatmeal	(= 12% ,, ,,)	—104	,, ,,
2 pints milk	(= 3% ,, ,,)	—525	,, ,,
1½ oz. cheese	(= 33% ,, ,,)	—211	,, ,,
[1]1½ oz. pulses	(= 22% ,, ,,)	—141	,, ,,
	Total ...	1,325	,, ,,

[1] These percentages apply to these foods when dry before cooking; when mentioned in the table of meals further on, they are of course weighed with a large quantity of water which diminishes their percentage value.

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and the remaining 145 grains will probably be made up out of the cereal or other vegetable products he takes as puddings and the garden vegetables and fruits ordinarily consumed.

Now many modifications of this diet are possible, and the best plan is, I think, for each individual to take that which suits his own taste.

Some find cheese convenient and portable, and live largely on bread and cheese; others prefer to drink a large quantity of milk or to take it with other foods; and those who are stout or incline to become so will have to skim their milk, or even leave it entirely out of the diet list, substituting an equivalent quantity of pulses, which are poor in fats.

For my part I prefer to take almost the whole of the substances mentioned above, but I vary the quantities of each constituent from time to time, in accordance with my feelings and preferences, and in summer I incline to diminish the pulses and substitute an increased allowance of fresh fruit and vegetables for them; I also eat somewhat largely of puddings and of rice in various forms and dishes.

When appetite is very good, which generally means when exercise and fresh air are plentiful, the quantities of the more nourishing foods (milk, cheese and pulses) should be diminished, because their place is taken by the increased quantity of bread, cereal foods, fruits and vegetables then naturally consumed, and conversely when appetite is poor, milk, cheese, and pulses may have to be increased, because less of the other things are taken.

If these points are not attended to we may get either too much nitrogen (urea and uric acid), as shown in fig. 65, or too little, with general debility and asthenia, as shown in the early part of fig. 64.

But there are difficulties in the way of this diet, and they are chiefly those of habit; for by many years of gradually changing custom we have got out of the habit of eating bread stuffs in sufficient quantity, and have got into the habit of eating animal tissues to excess, led away to our ruin by their stimulant effects; and these habits have reacted on the production and preparation of our foods, so that our bread-stuffs and cereal foods are not so numerous, so well prepared, so pure and nutritious, or so well known as they ought to be; while our animal foods are more numerous, more carefully and expensively prepared, are everywhere thrust on our attention, and are better known than they ought to be.

But habits cannot be changed in a day, and many of those who rush off to try and change them, leave off meat without being able to get into the habit of eating sufficient cheese, pulses, and bread

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stuffs, or drinking or otherwise consuming sufficient milk, and simply starve as the result.

Now this is a great difficulty, but if we look it square in the face we shall at once see that it is not an insuperable difficulty, for it is possible to retrace our steps and go back by the road we have come, and except in the case of a few people, where habit has become second nature, this can be done gradually and with care.

Bread stuffs, cereal foods, pulses, nuts, and the numerous foods prepared from these can be gradually increased, and the habit of eating them re-acquired, and then, when it is clear that a sufficient quantity of these can be taken, animal food can be reduced and left off; as in many other things, it is necessary to walk before we can run.

There are some who will not alter their diet however easy it may become to do so, and of these I am accustomed to say, that if their disease was anything like as severe as mine was before I altered my diet, they would soon find the necessary energy to make the change.

I will now give an outline of my own diet, which serves to keep my urea at or about the required level.

BREAKFAST.

Bread and toast	3 oz.
Butter	2 oz.
Porridge, mixed with butter and salt	8¼ oz.
Jam	1½ oz.
Milk, including that taken with porridge	1 pint

LUNCH.

Soup (containing peas, milk, and butter)	10 oz.
Bread	2¾ oz.
Pulses as cooked	3 oz.
Butter	2 oz.
Bread and butter pudding	4¼ oz.
Cheese	1½ oz.
Milk	6 oz.
Fruit	2 oz.

AFTERNOON TEA.

Bread and butter sandwiches, with mustard and cress or cucumber	3 oz.
Milk—warm in winter, cold in summer	4 oz.

SUPPER.

Savoury rice or macaroni cheese	3 oz.
Scones	2½ oz.
Butter	2 oz.
Rice pudding	4¼ oz.
Fruit	5 oz.
Sugar with fruit	2 oz.
Milk	6-10 oz.

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This would add up as about :—

Bread	11½ oz.
Porridge, rice, and peas as cooked[1]	18 oz.
Butter	7 oz.
Milk	40 oz.
Cheese	1½ oz.

With jam, sugar, potatoes, and fruit in addition.

There is probably here quite enough nitrogen to furnish 437 grs. of urea, which is 3½ grs. per pound on my ordinary weight, and at the time when these quantities were weighed I was excreting day after day somewhere about that quantity.

On the other hand, it is quite clear that when I used to live on so-called ordinary diet, I took more animal food than was at all necessary according to physiology, for my urea was then often at or above 500 grs. a day, and my weight about the same as at present, and I believe that a very large number of people are doing the same thing that I was.

I will now go through the meals again and point out some of the ways in which the diet can be varied, and I may say that I never was and never will be a good bread eater, I was brought up on too much meat when I was young, and never properly acquired the habit of eating bread, so that I have had difficulties with this diet which some people would never have to encounter.

Breakfast.—Bread and toast can be varied with rolls, scones, baps, oat-cakes.

Porridge can be made of various meals, coarse or fine, of quaker oats, H.O., or hominy.

Milk not eaten with the porridge is drunk warm in winter or cold in summer, but many people can take it hot best.

Lunch.—Soup can be made from almost any vegetable with the addition of milk and butter; receipts may be found in "Maigre Cookery" by Sydney Lear, Stanford, London, and many cooks will soon find out how to use other vegetables in the same way.

Many of these soups have extremely pleasant and delicate flavours, and offer greater variety in this way than can be obtained from meat, which largely overpowers other flavours.

Bread can be varied as above-mentioned, and biscuits can be substituted with cheese.

Pulses require long cooking, and haricot beans must have their skins removed before cooking, which is done by soaking them for a short time in boiling water or a longer time in cold water and then

[1] See previous note on p. 615.

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rubbing them off. Pulses should also be eaten only in small quantities at first by those unaccustomed to them as they may cause diarrhœa, and when insufficiently cooked they cause wind and dyspepsia.

Rice can be varied with such things as barley or macaroni, and these can be first boiled and then fried with butter and form a course by themselves, with which a little potato or other vegetable may be eaten.

I take no more of these latter, however, than an ordinary meat-eater would, often not so much, while the barley, macaroni or rice are an important part of the meal and make up for my small powers of bread eating.

Puddings, tarts, stewed fruit, &c., can be taken in the same way as by meat eaters, and my diet in this matter is the same as theirs.

Cheese may be considerably increased if necessary, but I have not been in the habit of eating it largely.

Fruit comes last, and is eaten freely to any extent for which there is appetite.

Milk is often taken with the pudding, but it may be taken alone.

Afternoon Tea.—All kinds of nice vegetable sandwiches can be devised which are much more appetising and refreshing than anything made with beef or mutton.

Supper.—Vegetables are, as above, often left out at this meal (and indeed it will be seen that I make no attempt to live on garden vegetables) in favour of rice, macaroni, scones and bread stuffs.

Puddings are the same as those of ordinary diet, except that eggs are left out.

Fruit is not neglected, but eaten to about the same extent as by meat eaters; in the above-mentioned supper it consisted of strawberries and cherries, cream and sugar being added to the former.

I myself make but little use of nuts, but they are, no doubt, very valuable foods and might, if necessary, be increased, and biscuits and various foods made from them can be used as additions to the diet. They have the disadvantage of being relatively expensive, but an increased demand would, no doubt, soon reduce the price.

It thus appears that I live on bread and cereal produce, which might be varied, if necessary, to a much greater extent than is above indicated, with milk, cheese, pulses, and a liberal allowance of butter, and that to these are added a little vegetable and a fair quantity of fruit. Gluten also may be obtained in the form of powder, and if the diet is not well taken so that more albumens are required, a certain quantity of it can be added to various puddings and prepared foods, greatly increasing the amount of nourishment they contain; it can also be made into very nice biscuits by the following receipt—16 oz.

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gluten, 8 oz. butter, 4 oz. sugar. I am indebted for this information about gluten to my friend, Mr. H. Higgins, of Cambridge, who has made it a subject of special study. He uses gluten flour made by Farwell and Rhines, Watertown, N.Y.[1]

I think it must be acknowledged that my nitrogen is sufficient, and could easily be increased if necessary, and that I do not starve, and have plenty of variety in food.

There are some who tell us that they cannot digest milk, or that they find it very constipating; as to digestion I think there are very few indeed who cannot digest a fair quantity if it is taken mixed with other things, as porridge or pudding, while hardly anyone would be free from discomfort who drank a quart of it by itself.

As to constipation, there are few things more constipating than meat, and if milk is added to a meat diet it no doubt increases this constipation, but with a diet such as that given above there are abundant residues for the intestines to act upon, so that constipation is quite rare, and the taking of a fair quantity of milk does not suffice to produce it.

But while most uric acid troubles are due to introduction of uric acid formed outside the body, it is also quite possible to suffer from excess of it in the blood if the formation in the body is excessive and if all that is there formed is not excreted.

Now, as uric acid is always formed as far as we know only in the relation to urea of 1 to 35, there will be no excessive formation of uric acid unless there is also excessive formation of urea; unless, in fact, more albumen is taken in than the body requires for its nutrition, or more than will form 3·5 grs. of urea for each pound of body weight per day.

But such increased intake of albumen and excessive formation of urea and uric acid entail also increased formation of acids, and these last, by diminishing the alkalinity of the blood, bring about defective excretion of uric acid; thus excessive formation of uric acid is generally accompanied by defective elimination, and these two causes working together soon produce an accumulation in the body which eventually comes through the blood, or is driven out of it into the fibrous tissues, producing trouble.

Now, when 3·5 grs. of urea are produced for each pound of body weight per day, 35 grs. of urea and 1 gr. of uric acid are produced for each 10 lbs. of body weight; and if 7 grs. of urea are produced

[1] To be obtained in this country from Warner and Co., 86, Clerkenwell Road, London, E.C.

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for each pound, then 70 grs. of urea and 2 grs. of uric acid are produced for every 10 lbs. and though such a rate of production as this can only very rarely be met with except in children, it is by no means uncommon to find urea $1\frac{1}{2}$ or even 2 grs. above the physiological level of $3\frac{1}{2}$ grs. per pound.

Now this may be done on any diet, whether animal or vegetable, and those who do it will undoubtedly very soon come to have considerable excess of uric acid in their bodies, which sooner or later will produce its usual effects.

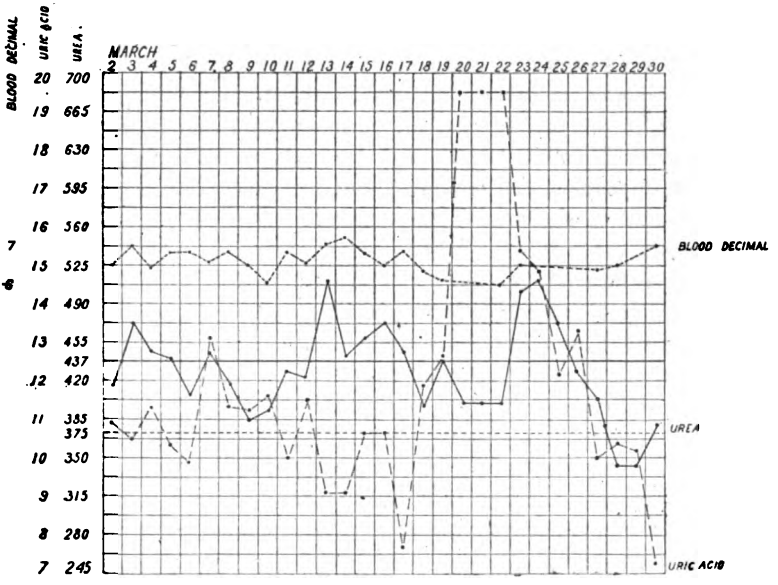

FIG. 65.—URIC ACID AND UREA EXCRETIONS AND THE BLOOD DECIMAL FROM DAY TO DAY; SHOWING THE EFFECTS OF DIET IN THE PRODUCTION OF AN ATTACK OF GOUT, AND ITS CURE BY SALICYLATES.

Now, fig. 65 shows that I have myself on some occasions taken too much albumen, and have consequently formed too much urea and too much uric acid; as a consequence of high acidity I have failed to excrete some of this uric acid, and have eventually suffered from some of the troubles it produces.

This figure also shows two lines across it, one a continuous one at the level of 437 grs. of urea, that is of 3·5 grs. per pound per day of my weight; and a broken line at the level of 375 grs. of urea, which is 3 grs. per pound per day of my body weight.

And the proper level for my urea is between these lines, if it is

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above them I am forming too much urea and too much uric acid, some of which I tend, especially in the cold season, to store or retain in the body; if it is below them I have less urea than is required for the best condition of nutrition, strength, and power of endurance.

As regards uric acid troubles, however, it is better to be below these lines than above them, but it is best of all, and not really very difficult to attain, to keep between them.

I shall now go on to describe this figure and explain how it was I got above the lines. In this figure we have really only to regard the two curves, the unbroken line urea, and the broken line of strokes the uric acid; the upper dotted line the blood decimal is merely given because I happened to be investigating it at the time this figure was evolving, in further illustration of what I have already said on the subject in chapter xii. With perhaps one exception on March 10 the blood decimal and the uric acid always move in opposite directions, and that one exception is probably to be explained in the way I have already pointed out in reference to fig. 45.[1]

We see then on following the urea line, that it was above 437 grs. level on March 3, 4, 5, 7 and 13 to 17, and again from 23rd to 25th, that it was only below the 375 gr. line for two days near the end of the figure.

The uric acid curve fell most below the urea exactly at those times when urea was highest, March 2 to 6 and 11 to 18, and this means, not that the natural formation of uric acid was altered, but that its excretion was hindered and diminished.

Now if we estimate the quantities by which uric acid fell short of urea on these days, which is easily done by adding up the number of grs. included between the lines of the two curves, thus, say 8 grs. from March 2 to 6 inclusive, and 22 grs. from March 11 to 17 inclusive, we get a total of 30 gr. of uric acid thus kept back and retained in the body.

Subtract from this the quantities by which uric acid exceeded urea, namely, rather less than ½ gr. on 7th, and rather more than ½ gr. on the two days 9th and 10th taken together, and ½ gr. on 18th, making a total of 1½ grs. of plus excretion, and 1·5 from 30 gives us a total retention in the body of 28·5 grs.

[1] I may say with regard to the average height of my blood decimal ·65 to ·7 as shown, that the great majority of those I see suffering from uric acid diseases have a blood decimal of only ·4 or ·5, and the enormous difference that this factor alone must make as regards function, nutrition, and the power of resisting microbic disease, is obvious to all physiologists.

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On the 19th, probably as the result of some fluctuations in acidity, as I took some alkali on the 17th to increase the excretion of uric acid, and this was unfortunately followed by a dinner with wine on the evening of 18th and some exposure to cold winds, I had a rheumatic pharyngitis and a slight similar affection of the larynx.

I may say that these are very common affections with me when I have too much uric acid about; and a little exposure to cold, or fluctuation in acidity otherwise caused, then suffice to bring them on.

Their pathology, as already explained, is that of gout of the fibrous tissues in any part of the body; they are due to a collection of uric acid in those tissues, and are relieved by anything (alkalies or salicylates) which increases its solubility and removes it from the tissues.

When I have no excess of uric acid in the body, neither cold acids, or anything else will produce such a pharyngitis or laryngitis.

But to return to the story of fig. 65. When I felt the slight pharyngo-laryngitis I tried to get rid of it by taking more alkali, but I suppose I did not take enough to counteract the exposure to cold or the rise of acidity produced by the wines; in any case the trouble increased and I began to feel rather ill with a rising temperature.

I then decided to give up alkalies and take salicylates, as with rising temperature their action would soon be the most satisfactory. I knew, however, that this was a dangerous course, for the reasons given in chapter xvi., and that I should undoubtedly be worse when the alkalies I had taken and the salicylates I intended to take, met and came into collision. But I had not at the time fully appreciated the meaning and extent of the retention shown in the early part of the figure, and therefore wrongly concluded that I had but little uric acid in my body and could afford to play with it.

The result, however, was a lesson which I shall remember for years, and I hope it will instruct many people besides myself, and save them from making a similar mistake.

On the evening of 19th the salicylates and alkalies met in the blood, the alkalies were still in some force from the doses taken in the morning, and the salicylates were just coming into the blood from the doses taken later, and the result of this was that my pharyngo-laryngeal trouble increased and extended downwards to the trachea, and there was also added a new centre of inflammation in the intestines, with severe pain in the region of the umbilicus.

With this on the 20th my temperature went up and up, first above 101° and then above 102°, so that in the early part of the day

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I was too ill to do anything but lie in bed as quiet as my cough would allow me to remain.

Towards evening, however, the salicylates which I continued began to get the best of it. The pain in the chest and abdomen moderated, and I was able to get some sleep; but I was not even yet over my troubles, as at about 4.0 a.m. on the morning of the 21st I woke to find myself with again very severe pain in the chest behind the sternum, and a frequent and painful cough (acute gout of the trachea and bronchi). Now the explanation of this relapse was fairly simple, for the salicylates had got the best of it on the previous evening with the rising acidity; but in the natural course of events there would be a fall of acidity in the early a.m. hours, and with this the dead point, as I have called it, between alkalies and salicylates would come once more into possession of the field (see p. 587).

I accordingly took some doses of ammonia and dilute acids, and reinforced the salicylates by repeated small doses, and in the course of an hour or two they again got the upper hand, and the gout passed off.

But while the struggle lasted I was in most severe pain, and had a frequent cough feeling as if it must tear my chest open, but with no expectoration, and I lay beyond and above my pain in no little fear of danger to life itself; for though I had had and recovered from a similar tracheo-bronchitis, I knew that I had in this case done what was very foolish, and I did not quite know how soon my drugs would relieve me, or how much damage might in the meantime be done to structures of vital importance.

For if there is one thing more than another certain, it is that these acute uratic inflammations of fibrous tissues regard neither persons nor places, but tend to spread along such tissues in any and every direction, affecting with equal indifference and impartiality both vital and non-vital organs, and I was uncomfortably conscious that close to what now felt like my blazing red-hot trachea and bronchi were the fibrous tissues of my pericardium and heart.

I had not only this constant burning pain in the affected structures, but the trachea and bronchi were as sensitive to cough as though they had been pounded with a hammer for half an hour. Fortunately for me the salicylates gradually again got the upper hand, the pain moderated, the cough became loose and effectual, and the expectoration of large mouthfuls of yellow pus gave ocular evidence of the acute inflammation that had been going on.

And now occurred a repetition of a result I have several times previously seen with salicylates, which were now in possession of the

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blood and getting the urates into solution from the inflamed tissues, and that was an alternation or migration, so to speak, of the gout from the trachea to the intestines and from the intestines to the trachea.

If I had too much clothing over me and kept the chest very warm, the pain would begin to return in it once more, and then if I threw off the clothes, so that there was more over the abdomen and less over the chest, the chest got better, but the pain in the abdomen tended to increase, so that I was forced to reduce clothing altogether and keep both as cool as possible, and then salicylates acted well, and I was soon comparatively free from pain.

This was obviously but a repetition of many previous experiences on myself and others as to the effects of heat in preventing the solvent action of salicylates on urates, and so preventing their relieving uratic irritation, whether called gout or rheumatism, as I have often already pointed out (see chapter xvi.).

I need not describe my convalescence at length. By the evening of the 22nd the salicylates had complete command of the situation, the pain was all gone, and the temperature was falling to about 100°, and next morning it was almost normal, and I was able to get up. Only a cough with considerable expectoration, becoming more fluid and less tenacious, and the passage of a considerable quantity of mucus with the first actions of the bowels, now testified to the existence of the inflammations which had raised the temperature and occasioned the pain.

It will be noted that the excretions of uric acid and urea in fig. 65 on March 20, 21, and 22 are in a straight line, and this is due to the fact that on these days I was much too ill to do anything but collect the urine, and I consequently estimated the excretion of these three days at once and divided the totals by three, so that the actual excretion was not exactly as shown; probably there was a comparatively small excretion of uric acid on the 20th while the salicylates and alkali were fighting and the temperature rising, and a much larger excretion on the 21st and 22nd when the salicylates got full power and were removing the materies morbi, to my infinite relief, both in body and mind.

If we count the grains between the curves of urea and uric acid on these three days, we find that uric acid exceeded its normal relation to urea by 8 grs. on each of them, or 24 grs. on the three, and if we add to that 1 gr. on the 23rd we have an excretion of 25 grs. out of the 28½ grs. known to have been retained in the body. *Sublata causâ tollitur effectus.*

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Had the salicylates been continued a day or two longer the whole might have been got out, and the fall of uric acid towards the end of the figure is only what generally occurs when salicylates are left off (I had perhaps better explain that this figure is but a part of a continuous curve going back for more than four months, and that as I kept a record of the total of retained uric acid day after day, I knew pretty well that there was little or none in my body before the beginning of March).

The rise of urea on the 23rd and 24th indicates, I think, that there was some defective formation of urea with the high uric acid on the 21st and 22nd, which was soon made up for and passed out with the improved circulation on the 23rd and 24th, just as I have shown to occur in the case of exercise when there is excess of uric acid available for solution in the blood, and also when the similarly produced defective combustion which we call Bright's disease, is put an end to by suitable treatment (see p. 455).

And now I have a story to tell as to the way in which I came to have the high urea shown in fig. 65, and how I consequently came to have both excessive formation of uric acid and its deficient excretion, thus accumulating nearly 30 grs. in my body with the disastrous results recorded above.

Just as the last (3rd) edition of this book was in preparation there appeared a very interesting work by Dr. George S. Keith, called "Plea for a Simpler Life,"[1] dealing largely with diet questions, and giving a most interesting account of his lifelong experiences in the matter.

From this it appears that he had also been a sufferer from migraine, which improved very greatly when he gave up butcher's meat in favour of fish, fowl, game and eggs in small quantities.

In this most interesting little book he dissents as much from the old remedies—bleeding, vomiting, purging, and sweating—as from the new—stimulants, tonics, and plenty of good food and wine—and believes rather in a middle course—rest in bed, water hot or cold to drink, and little or no food till there is some appetite and power of digestion. He narrates not a few very remarkable results with this treatment in cases of cerebral hæmorrhage, dyspepsia, bronchitis, phthisis, and especially in mental diseases, which are most interesting, and strongly support the results I have obtained and the suggestions I have made with reference to the causation and treatment of these diseases.

[1] Adam and Charles Black. London, 1896.

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And in a more recent work, "Fads of an Old Physician," 1897, he extends his arguments, and mentions more cases and more experiences, and he also compares my diet with his own, pointing out that I take far more food than he does. But though this is quite true, I am a younger man, and do much more work in a day than he does.

Dr. Keith also rather seems to infer that a great part of the treatment of uric acid disease is a small quantity of food, and that when this is attended to you may take small quantities of fish, fowl, and tea without harm.

I quite agree, as fig. 65 shows, that excess of nitrogen or albumen from any source will eventually produce trouble, for it will produce excessive formation of uric acid as well as defective excretion, as in this figure; but I think that where no excess of nitrogen is taken, greater freedom from uric acid disease and far better physical powers will be obtained by getting that nitrogen or albumen from substances which do not already contain uric acid or xanthin; and that, though Dr. Keith's experiences of giving up meat and substituting fish and fowl have been favourable, he has evidently not had complete immunity either from headache or from gout, and he would, in my opinion, have had much more complete immunity from both if he had obtained the nitrogen required for a physiological allowance of urea from sources which were entirely free from the poison, and if he did this he might eat any quantity of albumen necessary for strength and nutrition without the least fear of harm,

And now I come to the causes which led me to take too much albumen and to suffer so severely as already recorded; in "Fads of an Old Physician." Dr. Keith refers to another work on diet, by Dr. Dewey, of Meadville, Pennsylvania—"The true Science of Living;"[1] and the chief point in this book is that temporary complete starvation till there is once more a healthy appetite is the best cure for a host of dyspepsias, debilities, depression mental and bodily, headaches, and numerous other troubles, and that for similar less severe disturbances of nutrition the great remedy is to leave out the breakfast, so as to give the stomach a long rest of sixteen hours or more, with the object of allowing it to recuperate and accumulate secretions after the last meal of the previous day.

It seems from internal evidence in Dr. Dewey's book, a copy of

[1] Henry Bill Publishing Company and J. & J. Bumpus, Limited, Oxford Street, London, 1895.

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which I owe to the kindness of Dr. Keith, that his plans have been completely successful in a large number of cases, and it seems to me that his logic is unanswerable, and that in his main contentions he is perfectly right.

Having arrived at this conclusion, I proceeded forthwith to put the matter to the test of experience by placing myself on two meals a day—that is to say, I left out my breakfast, and the result was that I ate such a good lunch at 1.0 p.m. that it was impossible to take anything more till dinner time, 7.30 or 8.0 p.m., so that I reduced myself at once from four meals a day to two.

The result was exactly what Dr. Dewey describes. I felt extremely bright and well in the morning, and capable of very good work, both mental and bodily. At 1.0 p.m. I had keen hunger, even for dry bread ; such hunger as I had not experienced for years. After lunch (breakfast) I felt a little bit dull and occasionally sleepy, and the mental work of the first hour or two after it was not as good as usual. About 5 o'clock p.m., I was very thirsty, and had to have a drink of water, but there was not the least desire for food till several hours later, though by 7.30 or 8.0 p.m. I was able to manage another fairly good meal; and thus my meals automatically, so to speak, reduced themselves to two.

The effect of this change of meal times was, I think, unquestionably that my stomach and intestines did better work, the girth of the abdomen diminished, I think from the absence of undigested residues and the comparative absence of flatus.

The fæces diminished in bulk, and I experienced a general stimulation of nutrition and strength. The quantity of food taken was somewhat increased, and urea and acidity went up in spite of my somewhat feeble attempts to reduce the quantities taken, and no doubt, having a good appetite at 1.0 p.m., I took more pulses than I should have taken on the four meals a day plan.

As a result of all this I got high urea and acidity, and excessive formation of uric acid corrresponding to the excess of urea, and, as fig. 65 shows, retention of uric acid. The rest of the story has been told.

The result then was to leave on my mind no doubt that in Dr. Dewey's plan of two meals a day in place of four we have a most powerful stimulant to digestion and nutrition. Digestion is more perfect, just as with better appetite one would expect it to be, and nutrition is stimulated ; the fire burns more brightly and combustion and absorption are more perfect.

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That it led me into so great misfortune was no fault of the plan, but was due to my own folly in allowing my relatively huge appetite to fall to work on such highly nitrogenous food as pulses, cheese, and milk, which were appropriate enough for the more feeble digestion and lessened appetite and nutrition of four meals a day, but contained far too much nitrogen for the stimulated appetite and nutrition, and improved digestion and absorption of two meals a day.

If I had let my new appetite have its fling on less nourishing fruits and vegetables, and taken only my ordinary allowance of pulses, milk, and cheese, all would have been well, and fig. 65 would never have been evolved or published, and I should have escaped much pain; but it is through these things we learn, and I have learned a very great deal from this sharp lesson in diet.

First of all I have learned exactly how two meals a day cures dyspepsia, and the headaches, mental depression, &c., dependent upon it.

My verdict is that the dyspepsia is cured just as Dr. Dewey says, by resting the stomach and enabling it to do much better work, and that it is prepared to do this is shown by the presence of keen hunger otherwise quite unknown. I certainly had not experienced such dry bread hunger as I call it for years. If anything will demonstrate the insane folly of stuffing a dyspeptic stomach with fresh food every three hours, an experience of this kind ought to do it. Then the cure of the headaches, depression, &c., is the simple result of the stimulus to digestion and nutrition, for acidity and urea rise and the blood is promptly (as my case showed only too effectually) cleared of uric acid, and this no doubt is still more marked in Dr. Dewey's patients, as they are given animal flesh in any quantity and in any form they like. With such stimulation it would be quite impossible for any uric acid to get into the blood and remain there; hence headache and mental depression vanish and remain absent as long as the stimulation lasts.

But these patients, while thus taking meat, are introducing uric acid in their food, as well as forming it in their body in excess, and they are retaining it in large quantities from both sources; and if at any time the stimulation of two meals a day falls through—if any accident or shock depresses them beyond the power of two meals to revive them—then I do not envy them the result that must ensue from all the store of uric acid they are thus accumulating.

I should mention that it was no doubt partly because I gave up or became irregular with my two meals a day about March 17 and 18 (fig. 65) that I got the uric acid through my blood and

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suffered from the gout and other troubles; but my experience shows that my uric acid was not destroyed or burnt up by the improved nutrition, but was merely retained in the body ready to get into the blood when the conditions were favourable for this. And Dr. Dewey's patients would have been worse off than I was, for they were introducing uric acid with their food, as well as forming it in excess and retaining it.

While, therefore, I quite appreciate the value of Dr. Dewey's plan of two meals a day as regards the treatment of gastric feebleness, debility, and dyspepsia, that plan does not in any way prevent the evil effects of uric acid on the body and blood; but, acting as a stimulant to nutrition, it keeps the blood clear so long as the stimulation lasts. But if this plan is used in combination with a uric acid free diet, and if proper precautions are taken to avoid the consumption of excess of albumen in the unaccustomed pleasure of satisfying a keen appetite, one may obtain freedom from uric acid both for the present and for the future, in that there is neither excessive formation nor unnecessary introduction, and this without sacrificing any of the advantages arising from the stimulus to digestion and nutrition of two meals a day in place of four.

It may seem extraordinary to those who look at the matter merely from the outside, that almost the only danger attendant on taking two meals a day in place of four is that of over-eating yourself.

As a result of these experiences in my own person, I now make use of Dr. Dewey's plan for those of my patients who suffer from dyspepsia and deficient appetite, and would thus be in an unfavourable condition for beginning a uric acid free diet.

Such a case cannot take milk, has dyspepsia from cheese, and terrible wind and pain after the smallest quantity of pulses; but after a few weeks on ordinary diet, with only two meals a day, appetite is so much better and digestion is so vigorous, that all the above foods can often be freely taken and easily and painlessly digested.

It is a good rule to eat slowly, for man does not live by what he eats, but only by what he digests. Thus vegetable food, if not well chewed and mixed with saliva, ferments instead of digesting, and again if so much is taken as to distend the stomach digestion may be brought to a stand, and fermentation and putrefaction may take its place. In both these ways, then, eating slowly will do good and prevent harm, and it is quite possible for a man to be better nourished on a little food eaten slowly than on a great deal eaten quickly.

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I have also seen several cases where people appeared to be under-nourished on my uric acid free diet taken in four meals or more in the day; but when the same foods and the same quantities have been taken in three meals a day, or sometimes better still in two, they have with better appetite done better digestive work, have absorbed more of it into their blood and passed less of it through them undigested, and consequently have been much better nourished. It is quite possible also to be under-nourished from the above causes when the quantities of albumens swallowed are considerably in excess of those required for body weight. These people may starve and die as Dr. Dewey (previous reference) shows, not from want of food but from digestion being constantly overpowered by its excess. Then again, a diet which consists so largely of fruit and vegetable products will keep the blood well supplied with alkalies, and so all the uric acid which is formed will remain in solution and be excreted, and there will be no storage or accumulation in the body, and not only will there be no storage, but the stores and accumulations laid down on the preceding ordinary diet will be gradually got into solution and passed out of the body.

In all these ways, then, we shall get the uric acid in the body and blood under our control, and so long as we keep up this control we shall find that we have prevented the diseases which are due to its presence in excess, and this is the real and ultimate test of the truth or falsehood of all that I have said on the subject.

Before going further there is one good old fallacy—the offspring of imperfect observation—to which I must again devote a little attention.

Several years ago (*Brit. Med. Journal*, 1888, vol. ii., pp. 10 and 11) I pointed out that Sir A. Garrod had fallen into an error of some importance in his argument regarding the results in a table which he quotes from Lehmann.

From this table it may be seen that the uric acid urea relation on a

Mixed diet is	1 — 29.
Animal diet	1 — 38.
Vegetable diet	1 — 22.

And Sir A. Garrod draws from this the inference that uric acid is not so much influenced by the nature of the food as urea is, and further, that animal diet does not increase the formation of urate, but rather the reverse, while a vegetable diet does increase it.

But these figures refer only to short periods of time. They refer,

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therefore, to excretion merely, and tell us nothing whatever about formation and introduction.

Undoubtedly the first effect of animal diet, as of uric acid itself, is to diminish the excretion of uric acid because it raises the acidity of the urine and diminishes the alkalinity of the blood (p. 107), and conversely a vegetable diet increases the excretion of urate because it lowers acidity: but if these investigations had been continued for weeks and months straight on, it would have been seen that the diminished excretion on animal diet would have been balanced later on by a plus excretion of more than the equivalent amount, and the plus excretion on vegetable diet would gradually have fallen towards the level of formation, 1—35 or 1—40, when all previous accumulations had been removed.

As a matter of fact, formation never varied in relation to urea one jot, being the whole time at or about 1—35 or 1—40, only on animal diet part of the urate formed and introduced failed to be excreted and was kept back and retained in the body, while on the vegetable diet some little urate previously formed obtained enough solvent alkali to effect its solution and excretion.

The figures are, I doubt not, perfectly correct, and agree in every way with my own results; they refer, however, only to short periods of time, and owing to the prevailing idea of excessive formation of urate the conclusions drawn from them are, I believe, erroneous in the extreme (see also p. 75).

Liebermeister (*Vorlesungen uber Specielle Pathologie u. Therapie*, vol. iii., p. 42) falls into similar error, as he says (my translation) in early times it used to be thought that in gout one ought to limit the use of proteid substances as much as possible in order to put a stop to the excessive formation of uric acid. One forgot, however, in taking this simple view of the matter, that it is not of much consequence how much nitrogenous material is oxidised, but only whether it is more or less completely oxidised; and he goes on to say a healthy man excretes so much urea and so much uric acid in twenty-four hours, but an increased consumption of proteids increases to a corresponding extent the urea but not the uric acid.

That is to say, he infers that because the *excretion* of urate is not increased by a meat diet, relatively less urate is formed, or, as he would probably put it, it is further oxidised into urea and got rid of.

The real fact is, I believe, that urate is *formed* in proportion to urea just as it is on any other diet, and animal food also introduces some urate ready formed, but excretion falls short of formation and introduction owing to rising acidity, and some part of that formed

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and introduced is held back in the body, and can be washed out and produced at any future time by administering a dose of salicylate, alkali, or other solvent (see fig. 65); or, if the curves of excretion are watched sufficiently long, it may come out of itself when from some natural cause the acidity falls.

I think, therefore, that once for all we may free our minds from this bugbear of formation, oxidation, and other more or less theoretical myths, and believe that for all practical purposes uric acid is always, and on all diets, formed in the relation to urea of about 1—35, while certain foods also introduce a more or less important quantity of uric acid or xanthin ready formed (for some interesting results obtained by administering hypoxanthin to animals, see Lea, "Chemical Basis of the Animal Body," p. 182, and compare this with my remarks in ch. iii., p. 113).

I am interested to see in this connection that a recent writer in the *Journal of Physiology* (vol. xxii., p. 146), W. J. S. Jerome, gives as one of his conclusions after an investigation of the subject, that the daily output of uric acid is probably due to the larger or smaller amount of the alloxur-holding bodies (*i.e.*, xanthins absorbed from the food; this conclusion being practically identical with that I have drawn from my own researches published in the same journal, vol. xv.

See also the *New York Medical Journal*, 1896, vol. ii., p. 578, for the record of toxic symptoms produced in a rabbit by the administration of hypoxanthin in the food. I have often produced some similar symptoms in myself, and I have not the least doubt that I could reproduce them in anyone who would volunteer a *corpus vile* for the purpose.

Oxidation is no doubt important, and oxygen is occasionally useful, and I have consumed a lot of it experimentally. When I managed to raise the acidity of the urine and diminish the alkalinity of the blood, I cleared that fluid of uric acid and no doubt improved nutrition, combustion and metabolism; but it is not nearly so powerful in this way as a few fractions of a grain of mercury, or one of its salts. And I do not for a moment believe that all the oxygen and oxidation in the world will alter in the least the relative formation of uric acid and urea in the human body; and the diseases from which we suffer have often far more to do with introduction than formation.

Whether uric acid will be excreted in the relation 1 to 35 is a totally different question, for excretion, as I have pointed out, can be varied at pleasure in almost any direction, and within very con-

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siderable limits. And it is by taking excretion as proof of formation that the authors above quoted have fallen, I believe, into serious error. I do not assert that uric acid is never formed in excess of the relation to urea 1—35; my experience is too small to carry such a proposition; but I do assert, of all the diseases of which I have written, in so far as they are due to uric acid, that they are due to its accumulation in the body from large formation and introduction and failure of excretion; that I have never met with any evidence of formation in excess of the above ratio to urea, or any reason to think that all the urate I have met with could not have been accounted for by failure of excretion.

For my part, I return without hesitation to the doctrine of early times, and fight uric acid disease by reducing the introduction of uric acid, and where necessary, its formation also, believing that the clinical observation of Cullen, "that gout seldom attacked persons employed in constant bodily labour, or those who live much upon vegetable diet," is a more valuable guide in treatment than many more recent conclusions founded on imperfect observations. We now know that constant bodily labour facilitates excretion (figs. 39 and 40), while vegetable diet diminishes introduction as well as facilitating excretion.

I have now also the best of all proofs of the correctness of my reasoning in practically complete immunity from a disorder which formerly threatened to interfere seriously with my work.

Such a result must speak for itself, even if the theory on which its explanation is founded is destined eventually to give place to a better one, the product of still wider knowledge.

The late Professor Humphry says (*British Medical Journal*, 1888, vol. i., p. 512) that 62 per cent. of the aged take but little animal food, and I should link this with Cullen's observations, and the very deadly effects of many of the diseases mentioned in previous chapters.

In altering diet, however, it is necessary to exercise some care, especially in regard to the amount of urate that may be stored in the body. In a man of middle age or beyond it, who has lived heartily, without stinting either meat or wine, there is sure to be a large collection of urate in the body; and if his animal food is reduced, and his acidity runs down, this will be dissolved out and flood his blood; for weeks and months there may be a plus excretion of urate, and its results will be more evident than pleasant; he will worry you with continual complaints that he is getting weak, that he is dying, that he has headache, depression, &c., and may

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even talk of suicide. Similarly, in cases which have been put on what I regard as the most dangerous of all modern diet cures, that of meat and hot water, it is wiser to go slowly and get them back gradually on to ordinary flesh diet, and then from that on to a uric acid free diet with vegetables and fruits; but to make a sudden change on to this latter at once may bring about severe uricacidæmia and collæmia, with high blood pressure and all its most serious results, especially in those who are no longer young. In all cases also it is necessary to see that nutrition, strength and power of endurance are quite as good on the new diet as they were on the old; in the majority of cases they are very decidedly better on the new, but if there is the slightest suspicion of their not being so, some mistake is being made and the matter should be investigated. In other cases, where the accumulations are not so large, one may gain so much by stopping the large daily introduction that it is better to alter diet at once, especially to cut off soups, meat extracts, strong tea or coffee, giving perhaps a tonic or some drug which will cause a little retention and keep the blood moderately clear of uric acid for a little.

As I have said several times before (see *Practitioner*, April, 1891, p. 279), I believe that the great majority of Britons of the present day could live very healthy and hearty lives on such a diet as I recommend, if they would make a rational attempt to do so.

To get them to make the attempt, however, is generally the difficulty; they think the diet must be lowering, and believe that beef steaks and beer are necessary for their continued existence, and undoubtedly, where the change of diet is allowed to produce considerable uricacidæmia, the resulting mental depression, with languor and disinclination for exertion, are sufficient to give some support to their assertions.

But, as I have shown, such results are quite unnecessary; they are not due to the new diet, but to the amount of urate which has been accumulated on the old one, and to the fact that these people have become accustomed to a stimulating diet, just as they might have become accustomed to an allowance of alcohol, but few people would in these days allow this as an argument that alcohol is either a necessary food or a source of strength.

Another objection sometimes urged against the diet is that people tend to grow stout on it, and no doubt if they eat large quantities of butter, cream and fat cheese, and drink much milk this may be the case; but this is not a necessary part of the diet by any means, for milk may be skimmed or left out entirely, butter and cream may be

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avoided, and skim-milk cheese may be eaten in place of cream containing cheese. If it is necessary to leave out milk entirely its place may very well be taken by an equivalent amount of the pulses, which contain very little fat.

Further, I believe it is quite possible so to use this diet as to easily and simply reduce the body weight in those who are already too stout, and I have set about this in the following way. Find the approximate weight in pounds before the patient began to get too stout, give him a physiological allowance of albumens according to the rule given on p. 615, let him get the required albumens chiefly from pulses, gluten and skim-milk cheese, but otherwise entirely leave out both fats and starches, and let the metabolism feed on its own accumulated supplies. The effect of this will be a steady and continuous loss of weight without any loss of strength and nutrition, and this diet has all the advantages of the pure flesh diet, without its dangers, and without most of its difficulties.

With regard to this point and what I have already said in chapter xiv. as to the possibility of treating diabetes without animal flesh or eggs, that is, on a uric acid free diet, I may mention that a substance called "protene" has now been made from milk, which, while containing all its albumen is apparently free from sugar and fat, and is therefore a valuable source of albumens when the whole milk is inadmissible.

This protene can be obtained from Protene, Limited, 36, Welbeck Street, London, W., either as a powder or as bread or biscuits, and I have tried these myself and have found them by experience to be both palatable and nourishing. The protene powder can also be mixed with various articles of food to increase their nourishment value.

By the use of these things and other forms of albumen, such as gluten, which can also be obtained from the same company, it is now possible for a sufferer from either obesity or diabetes to obtain all the albumens required for his daily nutrition in a very few ounces of food; and these will be practically free from fat, sugar, and starch on the one hand, and uric acid and xanthin on the other.

As already said, I have great hopes of being able to do much good for sufferers from the above conditions by means of these substances, and indeed in some cases I have already done so; and have been able to reduce body weight by several stone in a few months, with ease and certainty, and with decided improvement in strength and nutrition.

As I have said, the difficulty is to get people to try; they

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are often so frightened by the proposal that they will make only a very half-hearted attempt, which is insufficient to carry them through any little troubles that they may meet with at first, into the smooth water beyond, when all accumulations of urate have been eliminated and introduction reduced. I have never seen anyone who wished to go back after arriving at this stage.

The amount of animal nitrogen to be allowed in any given case should be determined by the effects on urea. For slight troubles, such as headache or mental depression, when not severe, it may be sufficient to merely reduce considerably the amount of meat taken, replacing it by bread and milk. In epilepsy, on the other hand, it may be necessary to take no animal food, but milk, and not too much of that; and further, to purge pretty actively so as to cause wasting and loss of strength, as in the case I have mentioned (p. 219).

In Bright's disease we have not only to reduce the formation and introduction of uric acid, but we have to accommodate the deranged metabolism by giving albumen in that form which, according to the late Professor Semmola, requires least elaboration to fit it to become a natural constituent of the blood, namely, milk.

A good many people consider fruit and sugar, either mixed or separate, to be deadly poisons, and things which the gouty should altogether avoid; and I have no doubt that, as regards an ordinary mixed diet, this is perfectly true. If these things, directly or indirectly, raise and keep up the acidity by originating fermentation in the intestinal canal, they will, undoubtedly, tend to precipitate urates upon the joints, and do harm in any arthritis, which is due in part, or in whole, to urate irritation; but if the urate be first of all removed, and is not continually introduced in excess, they will have nothing to act upon, and will do little or no harm.

Some interesting points with regard to the possible effects of diet are brought out in the Reports of the Sanitary Commissioner, with the Government of India, and I owe these facts to the kind suggestion of my friend, Dr. de Watteville, that it might be worth while to investigate these Reports.

The following figures are from the Annual Report for 1892, issued in Calcutta in 1894, and they refer to the incidence of the diseases mentioned in the English and native armies respectively.

The English army numbered, according to the Report, 68,162, and the native army 145,340, and the ratio of English to native is about as 1—2·1.

My cousin, Surgeon-Colonel P. de H. Haig, I.M.S., informs me

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that the English army in India eats as much meat in a day as the Indian native army does in a week, man for man; that the native army lives chiefly on grain and rice, that they have a long service system, not short as for the English, and that the natives have been exposed to malaria from childhood.

Disease.	68,162 English.	145,340 Native.	Ratio, Eng. to Native.
Alcoholism	273	11	54 to 1
Rheumatic Fever	115	48	5 „ 1
Gout	13	9	3 „ 1
Megrim	7	57	1 „ 4
Epilepsy	73	63	2 „ 1
Melancholia	61	22	6 „ 1
Syncope	6	3	4 „ 1
Dyspepsia	1,087	454	4 „ 1
Typhlitis	32	16	4 „ 1
Colic	311	51	12 „ 1
Piles	452	196	4 „ 1
Congestion of Liver	660	117	12 „ 1
Ague Spleen	46	1,405	1 „ 14
Bright's Disease (all forms)	51	40	(nearly) 3 „ 1
Suicides	25	9	6 „ 1
Ague	28,842	65,944	1 „ 1
Anæmia	209	909	1 „ 2
Bronchitis	1,925	4,234	1 „ 1

Now we see that in the case of almost every disease treated of in this book, there is a more or less large excess of incidence on the meat eating English, as compared with the rice and grain eating native.

There is an apparent exception in the case of migraine, but it is evident that this is not the disease treated of in chapter vi., but is really a neuralgia related to malaria, and like ague spleen, more frequent in the native army, which is more saturated with malaria.

The ratio of alcoholism is enormous, but probably factors of race and religion come in here as well as diet, but in any case it is not a record of which we need be proud.

Rheumatic fever and gout are fairly prominent, epilepsy is 2—1, while melancholia shows much greater excess; and probably the exposure of the English to heat from which they have not been accustomed to protect themselves will account for this, but none the less it powerfully endorses chapter viii.

Syncope again, 4—1, and yet we are accustomed to look upon the Englishman as strong in his beef eating, and the native as thin and weak.

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Dyspepsia 4—1, and yet the English are, I suppose, younger men than the natives, and dyspepsia, as a whole, tends to increase with age.

One cannot but be struck also with the enormous incidence of dyspepsia in girls just at the age when as I have shown (fig. 51) they have most uricacidæmia, and the comparative absence of similar troubles in boys; then again on ordinary diet dyspepsia increases in both sexes after middle life, and so does uricacidæmia.

Typhlitis and colic are again remarkable records in relation to chapter x.

Piles and congestion of the liver tell the same tale, though no doubt they are in part related to the large alcohol record above.

Ague spleen is related to the long exposure of the native army, and is also connected with migraine above, and anæmia further on; the last named being no doubt specially related to the large fluctuations in urate excretion, which recurrent malaria with enlarged spleen will occasion.

Bright's disease and suicide again represent the effects of capillaries obstructed by uric acid, and show a great excess among the English meat eaters; and for suicide we may notice that the ratio is the same as that for melancholia.

Lastly, bronchitis is nearly the same for both; but inasmuch as the native army is composed of longer service, and, therefore, older men than the English, and as bronchitis generally increases with age, it is relatively less in the native than in the English army. I have no doubt that in such a record other factors besides diet will have to be allowed for, but it is very unlikely that any of these will account for the great differences in disease incidence all along the line, and I commend these facts to the careful consideration of those who believe that the Englishman's beef is the source of his health, strength, and powers of endurance, or his superiority over other races; it is at least clear that he has no superiority over them in the matter of disease incidence, and this is an important factor in efficiency.

I am indebted to my friend, Dr. E. G. Horder, who has spent a good many years in China, for the information that the great bulk of the Chinese eat about 3 ozs. or 4 ozs. of fish a day, while the rest of their diet consists of rice. He says they are fine, big, and strong men, and more than a match for the average or even a picked British sailor, the only Briton generally available for comparison; and he adds that their wounds heal easily and generally by first intention. A similar record with regard to the Turks as to their

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great powers of endurance and wonderful vitality in resisting wounds, is to be found in the recent numbers of the daily papers. Thus in the *Standard* of May 6, 1897, we find: "The doctors also remark upon the extreme rapidity with which their patients recover from their wounds, and attribute it to the abstemious lives they lead, drinking no wine and eating very little meat but plenty of vegetables."

Here again in England, do we not die younger, and in greater number than there is any necessity for? Are we not afflicted with an infinite number of diseases which cause far more pain and misery than is at all necessary? Are we not given to all kinds of debauchery and excess, and have we not huge asylums full of lunatics and prisons full of criminals.

I look upon all these things as serious and widespread diseases in the human race, and as I am not one of those who believe that Nature herself, if she had a free hand, would tend to destroy us, but rather to preserve what is good, and eliminate what is evil, and, further, cannot believe that the tendency to these evils is part of the ground plan of Nature's work, or that the unalterable bias to have headache, epilepsy, mental depression, mania, and their results—murder or suicide—alcoholism, morphinism, cocainism, &c., is originally implanted in our nerve centres, I am driven to the conclusion that not a few of these evils are the result of unnatural conditions, and that prominent among these is unnatural diet, the evil action of which we are now in a position to follow out more completely through a knowledge of the powerful effects of urates on the function and nutrition of the whole body.

Such a provisional conclusion is justified by my own experience and results. I was originally told that my tendency to headache, high arterial tension, and other evils, was inherited—in fact, a part of my structure and function, which, though it might be modified and relieved by drugs, could not be eradicated; and no one ever suggested a radical change of diet.

By great good fortune, and more or less by chance, I found out that a change of diet was the one thing needful, and what is practically complete cure has resulted. I have now only one subject for regret, namely, that I did not find this out earlier in life, as I cannot undo the evils and injuries that were accomplished while the warnings of functional disturbance remained unheeded through ignorance of their causation.

To a very large extent, therefore, I disbelieve in inherited weakness, innate delicacy, or transmitted neurosis, in so far as such expressions apply to the diseases mentioned in the preceding chapters.

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The only factor concerned with my headache that I inherited was probably a slight variation in the size and distribution of the arteries at the base of the brain, rendering my intra-cranial circulation specially liable to be affected by unduly high blood pressure;[1] the other factors in its causation were improper food, impure blood, and consequent increased blood pressure, but the improper food being done away with, the "neurosis" became a matter of history, in spite of the anatomical factor which remains as before. I notice also a very interesting clinical note by Dr. David Drummond, of Newcastle, in the *Lancet*, 1897, vol. i., p. 1,338, on "neurotic" symptoms of uric-acidæmia in the young, in which he exactly describes the headache, epilepsy, cold hands and feet, low surface temperature, high blood pressure, and slow pulse mentioned in previous chapters, and finds them associated with meat eating and excess of uric acid in the urine, and cured by milk diet, and, as he tells us he had formerly treated the neurotic element in such cases with unsatisfactory results, his observations confirm my own in every respect. He also notices a symptom which I have not noticed, namely, diminished knee jerks, apparently in association with mental and bodily depression and lethargy.

I believe that much the same argument applies to nearly every disease mentioned in this book, and that while certain anatomical or physiological peculiarities may undoubtedly dispose certain individuals to suffer sooner than others, or in one way rather than in another, nevertheless the food factor is common to all of them, and its adequate consideration and treatment will always result in prevention or cure. The first step towards this object is the full and complete recognition of the fact that for all practical purposes they are diet diseases, and that gout and rheumatism, for instance, may depend quite as much on the inheritance of the dollars necessary to obtain meat and wine as of any anatomical or physiological peculiarities.

Might it not be worth while to make a determined effort to treat our criminal diseased with a uric acid free diet? If the alteration in their cerebral circulation is functional, it will do more than anything else to remove it, and if after that has been done they look at life and the world from a different standpoint, the practical knowledge how to live cheaply on an unstimulating diet may be of no small advantage to them; and lastly, it will, or should, greatly diminish the cost of maintenance, and, if I mistake not, the cost of

[1] *Brain*, Spring and Summer Number, 1893, p. 250.

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disease and crime already presses heavily enough on the less diseased portions of the community. Then precisely the same will apply to our vast asylum and poor house populations; the inhabitants of the former must often owe their disease to unsuitable diet, acting in the manner depicted in previous chapters; and the tenants of the latter may owe their poverty in no small degree to a lifelong habit of spending their money on stimulation in place of nourishment, thus constantly losing both in power and pocket.

I see plenty of poor women who live from week's end to week's end on little but bread and butter; but the husbands of these women still think that it is impossible to do a labourer's work without beef and beer, and know but little of the nourishment values of cheese and pulses, a position about as far from the truth as it is possible for an ignorant man to arrive at. About one half of what the man spends on stimulants would provide both himself and his wife with all that nourishment requires. Then, in spite of his insular position, the British workman is even now suffering reverse after reverse at the hands of the foreigner, who has learned from stern necessity the lesson of cheap living.

I am very pleased also to be able to add that quite a large number of fellow-sufferers have now had experience similar to my own—not that the diet is successful in every case. I have never met with any treatment which could honestly lay claim to so large a proportion of cures. Some are unable to alter their diet, being unable to eat at all when a change is attempted; others apparently alter their diet and yet are not cured, but these cases are the exception, and require further investigation before anything definite can be said; and I sometimes find that such cases have been making the mistake of continuing a little meat or fish, or in the case of ladies some tea. On the other hand, a considerable number of sufferers in the profession have applied my suggestions to their own cases, and report that they have every reason to be pleased with the result. One of these concludes a letter recently received by saying: "Beyond doubt I have established the fact that much, if not all, of my ill-health and moral disturbances were caused by eating butcher meat, the metabolic products of which I was unable to eliminate."

Another professional patient writes, after narrating other cases in which the treatment has been equally successful: "Personally my debt to you and to the theory is a heavy one. Four years ago I was an old man at 37, with the enthusiasm and vigour of life quite crushed in me, retired to a pottering country practice to eke out a miserable existence. All that is now thrown to the winds, and I am

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back to town work in the fore front of the battle, and with the keenest enjoyment of life."

This record shows us in a few words how much those who do not lose their lives may yet lose in the mental and physical enjoyment of them, by remaining the slaves of diet and the victims of collæmia.

Speaking of morals reminds me of the very moderate and much needed warning given by Dr. Keith ("Fads of an Old Physician," ch. xiv.) with reference to the effects of high living on the morals of the young, which my own experience leads me to endorse most thoroughly (see also p. 129).[1]

I have also heard from my friend Dr. W. Young, of Wellington, N.Z., of the case of a man aged 50, who some three years ago suffered from headaches and loss of energy (collæmia of decline of life[2]), and then adopted a system of treatment by cold baths with abstinence from meat. The result was that he soon got a distaste for meat and left it off altogether, and Dr. Young, who met this man while attending his wife, goes on to say, "he is very pleased with the result of the three years' vegetarianism, and says that though during these three years he has lost weight, yet he feels stronger, and is more energetic and rarely has a headache. The improvement he attributed to the baths."

I think the author of the above-mentioned system is to be congratulated on his knowledge of human nature, for this man would not have altered his diet except to help the baths; and would have indignantly repudiated the suggestion that he was eating meat which did not agree with him. Of course he had been eating it all his life, and knew much better than that! The case is a beautiful illustration of the value of the oblique method in dealing with people who are absolutely ignorant and full of prejudice.

With regard to alcoholism, I think the vegetarians can make good their claim that the adoption of their diet does as much to cure this trouble as anything that is known, and the reason that it does so is simple enough.

Meat, as I have said on pp. 96, 107, is a stimulant, and causes a fluctuation in the excretion of uric acid; its stimulation is due to the diminished excretion or retention of uric acid, because, as we have

[1] I was interested to see that in a recent discussion in the *Lancet*, 1897, vol. ii., p. 685, on schoolboy morals one of the writers advocated a reduced allowance of meat; but I fear that the tide of custom at schools and colleges still runs strong in the opposite direction.

[2] See remarks on p. 254 on the most common age for suicide.

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seen, every drug which clears the blood of uric acid is a stimulant; but this is followed by an inevitable corresponding and more than corresponding depression, when the urate at first driven out of the blood gets back into it along with the urate introduced in the meat itself.

For the relief of this depression more meat must be taken, and when meat begins to fail in causing sufficient stimulation alcohol is added; when alcohol begins to fail morphine or cocaine are called in, and so on down the road to ruin.

Now vegetarianism cuts through this vicious circle at one blow by making it impossible for there ever again to be any great excess of uric acid in the blood, and so removing the cause of the depression which leads to the craving for stimulants.

But even this is not quite the whole story, for meat is not only a stimulant, it also causes thirst. We have seen that every drug that clears the blood of uric acid causes diuresis, that this leads to concentration of the blood, and that thirst is the expression of the blood's wants, and goes along with diuresis (p. 24); therefore the meat eater is always thirsty, and if he from one cause or another—occasional depression, it may be—acquires the bad habit of quenching his thirst with alcoholic drinks, he soon gets too much of them.

The vegetarian, on the other hand, is not often thirsty, because he is not subject to urate fluctuations and diuresis, and also because the fruits in his diet list themselves supply him with a very large amount of water.

In reference to the term vegetarian, it is evident that I am not a vegetarian in the strictest sense, because I take milk and depend upon that product largely for my nitrogen; on the other hand, I differ greatly from many who call themselves vegetarians in this country in not taking eggs, tea, coffee, cocoa and other vegetable substances which are stimulants because rich in xanthin compounds.

I am only concerned in these diets and isms in so far as they bear on the prevention and treatment of disease, and so far as these are concerned eggs are as bad as meat. I prefer therefore to call my diet "xanthin or uric acid free diet," to emphasise the points in which it differs from vegetarianism.

I am also decidedly of opinion that still better results would be obtained in the prevention and treatment of alcoholism if a uric acid free diet is substituted for a vegetarian one containing eggs and tea. The latter is nothing but a stimulant, and if stimulation is as I believe always wrong, it is doubly wrong in cases where it has already led to abuse.

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I will now say a few words as to the most useful drugs for clearing the blood of uric acid. Of the very numerous drugs which have this effect, I prefer the iodides, mercury in some form, or the iodide of mercury, or, if it is necessary to act quickly, the nitrites, or a subcutaneous injection of morphine.

If there is any good reason for not using mercury, other metals, as copper, zinc, silver or gold, or their salts, may be used with equally good results as regards uric acid; and I have no doubt that the tonic action of these and other metals is due to their effects on the solubility of uric acid.

The iodides seem to be specially useful where the effect has to be kept up over a long period, as in relieving the high tension of chronic Bright's disease. Mercury is useful in headache or mental depression, and iodides in asthma.

All these drugs, however, have the drawback that their action is followed by a rebound as soon as they are withdrawn; the uric acid which they clear out of the blood is not cleared out of the body, and as soon as the drug is withdrawn, the blood soon takes up the uric acid which has been accumulating during its action.

The best way out of this difficulty appears to be to alternate these drugs with a course of salicylate of soda, which eliminates the uric acid and prevents the accumulations from becoming very large.

And salicylates are themselves useful in lowering pulse tension and clearing the blood of uric acid: but their greatest effect in this direction takes a day or two to come out, for, during the first two days of their action, while the excretion of uric acid is very large, the urine is scanty and the capillaries are not so free as they would be under drugs of the mercury and iodide class, which clear the blood of uric acid within an hour or two at most.

Salicylates are useful also in headache to follow the mercury that has been used at first and remove the uric acid it has retained, and in the same way they may be useful in mental depression; and they may, as I have said, completely prevent fatigue, and will relieve it and its myalgic pains when present.

Salicylates are also very useful in some cases of asthma and in what are known as feverish colds. They will often relieve dyspepsia, especially if there is pain, and in what I have called gout of the intestines their effect is sometimes wonderful.

Similarly in anæmia they are of use, and apparently pass the uric acid through the blood without allowing it to do much harm, thus we see in fig. 65 that the blood decimal fell with the high uric acid

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on March 22 and the previous day, but the fall was proportionately small, and the same holds in paroxysmal hæmoglobinuria and Raynaud's disease, though in the attacks drugs belonging to the mercury and iodide class may be used in the first place.

In a word, it might almost be said that the iodide of mercury will cure all the diseases in the first fourteen chapters which are due to excess of uric acid in the blood, and that salicylates will cure the rest.

In albuminuria and Bright's disease, salicylates when they increase the excretion of uric acid often make the urine scanty and the albumen appears to be increased; but I have never been able to satisfy myself by actual estimations that there was in these cases any absolute increase of albumen. Still, in these diseases I generally prefer drugs of the iodide class, and only use salicylates occasionally to clear out accumulated urates.

Of the use of salicylates in rheumatism, glycosuria and diabetes I need hardly say any more, and in gout I believe that they have only to be given in proper cases and in sufficient doses to have their powers fully appreciated. I am glad to see that Professor Tyson, of Pennsylvania, considers them by far the best remedies in this disease (*Therapeutic Gazette*, November 15, 1895), and the cases narrated in chapter xvi., in which they failed, will serve to point out the conditions in which similar failure may be expected and the means of avoiding it.

It is not my purpose to go minutely into the drug treatment of each condition, for, in so far as any of these diseases are due to uric acid, the only real treatment is that by diet, which is both preventive and curative, while drugs for the most part (except the salicylates) relieve only for a time, and the trouble will return as soon as they are left off, and in not a few cases will be worse than if they had never been used.

If any of the troubles in the first fourteen chapters are associated with a slow high tension pulse and scanty urine the presumption is in favour of an excess of uric acid in the blood, and this and the urine may be examined; but if this is impossible, the temperature in the mouth and rectum may be taken as a guide (fig. 5), and drugs may be given which would have the effect of clearing the blood of uric acid and their effects on the temperature observed; or, on the other hand, caffeine or uric acid in some other form may be given to see if it eventually makes matters worse. When the diagnosis has thus been fortified, treatment by drugs and diet may be proceeded with.

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Dyspepsia may complicate any or all of these conditions, and when it is severe may to some extent prevent drugs from raising the acidity and clearing the blood of uric acid.

It will not, however, interfere with the drugs which are independent of acidity, such as mercury and other metals, whose uric acid compounds are insoluble, unless it prevents their absorption from the stomach and intestines, and in this case mercury can be administered in other ways.

In all cases, however, it is necessary to reckon with dyspepsia, and if possible to cure it; it is partly a cause and partly an effect of the excess of uric acid in the blood, and it fortunately happens that many of the drugs and the diet which is useful for uricacidæmia will also relieve or cure the dyspepsia; for instance, my so-called bilious attacks, and the dyspepsia which preceded and accompanied them, have disappeared along with my headaches.

Dyspepsia also must be kept in mind both in gout and rheumatism, and in chronic rheumatism it is often an important factor; it very probably keeps up more or less constant excess of uric acid in the blood (hence its important effects in the production of anæmia), and then, owing to formation of acids, exposure to cold, or other cause, a rise of acidity retains some of it from time to time in the joints and increases their irritation. Dyspepsia may also be treated by altering the meals in the way described with reference to fig. 65.

The treatment of uræmia is, I think, the treatment of high blood pressure, together with more or less œdema of the membranes and excess of cerebro-spinal fluid, which have been caused by the high blood pressure; the treatment of the high blood pressure may be the same here as in other conditions; but it may be necessary to do something more to remove the œdema, and it seems probable that venesection would be the most likely thing to succeed, for it would not only complete the reduction of blood pressure, but would probably cause the blood to take up available fluid from all directions, and we know that morphine and venesection have been found useful in this and kindred conditions. Uræmia also has occasionally been observed to terminate in an attack of gout, which of course would mean the practical clearing of uric acid out of the blood and relief of high blood pressure (see paper by the late Dr. Ralfe in *Transactions of the Medical Society of London*, vol. xvi., p. 216, and *Lancet*, 1893, vol. i., p. 415, also case in *Lancet*, 1889, vol. ii., p. 1,118).

I have mentioned in several places (pp. 43, 111, 197, and 206) some points in the pathology of gravel and stone, and I shall now

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merely remark that whatever the influence of other factors, an excessive excretion of uric acid is not very rarely the most important point in their causation.

Thus they are met with in old people who have suffered for years from gout and other signs of excess of uric acid in their body and blood, and are a natural result of failing metabolism in such people. Thus I have explained that those who have much urate in their joints may, as appetite and digestion fail and their acidity runs down, excrete for weeks and months an excess of uric acid till the joints which at one time were full of urates, show nothing but empty erosions of cartilage (see p. 520).

As the excess of uric acid from this source passes through the blood, it obstructs the capillaries and diminishes the flow of water from the kidneys, so that we get a large excretion of urates and very little water to carry it off, and it is little wonder that some of this urate is occasionally deposited in the kidney or the passages below it; and as I have shown in reference to fig. 55, it is the uric acid which controls the excretion of water, and not the water the excretion of uric acid.

Now this is a very painful and troublesome condition, and one with which it is very difficult to deal satisfactorily; thus it may be difficult to stop the plus excretion of urates, for the patient is often so feeble and his acidity so low that acids are overpowered; but mercury and iodides will act, and these will not only diminish the excretion of urates, but will, at the same time, increase the excretion of water. Soda and potash may be given, but they will not increase the water, and will increase probably the actual excretion of uric acid.

The urates are probably doing no harm in the joints, and nothing will be lost by letting them stay there a little longer, or come out into the blood and urine more gradually, so that I am inclined to think that the iodides form the best line of treatment to adopt. I am here speaking merely of the greater or less excretion of urates from gouty joints and other places of deposit in the body, and not of the treatment of a calculus in the kidney or bladder already formed; the line of treatment I suggest is intended to prevent their formation if possible.

It is an obvious conclusion from my reasoning that if a patient such as we find thus suffering from gravel in old age had altered his diet, in the way I am suggesting, twenty or thirty years before, he would in all probability never have suffered either from gout or from gravel.

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I am indebted to my friend Surgeon-Captain Ernest Roberts, I.M.S., for the following interesting observations with regard to the effects of diet on the incidence of calculus in India.

Among the poorly nourished, rice eating population it is rare. Among the wheat eating, meat eating and generally better fed provinces it is frequent; and in these provinces it is specially common among the men and boys, rare among the women and girls; and this is largely due to diet, for the men feed best and the boys with them, the women have their leavings, and the girls what they can get; the last-named being very little thought of, and badly fed.

It seems to me that this is extremely interesting, for in the meat eating provinces there is most introduction of uric acid, and those introduce most who are best fed (men and boys), and those introduce least who are least well fed (women and girls): and then the warm climate of India conduces to high alkalinity of the blood and the relatively rapid passage through it of all the uric acid introduced.

During the discussion of a paper which I read at the Medical Society in November, 1896, and in which I suggested that "the uric acid diathesis" is a myth, inasmuch as all the diseases referred to it are really due either to the excessive introduction of ready formed uric acid or the excessive consumption of albuminous food, both of which dietetic errors can be corrected, and the diseases due to them removed. I was asked by Mr. Freyer, who appeared as a champion of the "diathesis," how it was that many of the natives of India, who lived on exactly the kind of food I advised, yet suffered severely from stone? After what I have said with regard to the effects of excess of albuminous food (*i.e.*, of excess of quantity without reference to quality), and especially after my remarks on fig. 65, I do not think that the question requires much answer here; but the discussion thus begun was continued afterwards in the *British Medical Journal*, and was brought to a close with the publication of the most interesting letter of my friend, Surgeon-Captain E. Roberts (*British Medical Journal*, 1897, vol. i., p. 625), and in this discussion several facts of considerable interest were brought to the surface.

First of all it became evident that in spite of adverse criticisms the above-mentioned habits of the natives in feeding the men and boys best really exist, and no doubt account both for some extra introduction of uric acid as well as possibly for some excess in albuminates in males as compared with females. That more meat is really eaten by the natives of India than might be supposed, that large numbers of Mohammedans eat it regularly, and that the lower

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caste of Hindus take it whenever they can get it; and I am also indebted for corroborative evidence on these points to my friend, Dr. Bonus, and his brother, General Bonus, who served in India for many years in various official positions, bringing him into contact with the natives in various parts of the empire.

And, speaking generally, it seems to be just in those meat eating portions of the population that stone is most common. Further, Surgeon-Captain Roberts shows in the letter above mentioned that stone is most common in the districts where wheat is the staple food, and least common where rice is the most important food, and I may mention that Parkes gives the percentage of albuminates in rice as 5, while in wheat flour he gives it as 11, or more than double, and it is thus evident that the wheat eating population are much more likely to get excess of albuminates than the rice eating (see also remarks in chapter viii., p. 278, on "Causation of Fatigue and Rheumatism in Horses").

Further, it is evident from statistics kindly sent me by Surgeon-Captain Roberts, and which are extracted from a paper on "Vesical Calculus in India," which he presented to the First Indian Medical Congress in December, 1894, that the diet of the native soldier in India, though containing no meat, does, nevertheless, contain nearly one quarter more albuminates than the diet of the European soldier, and also that in some parts where certain kinds of pulses are plentiful and are freely eaten the diet of the natives contains a still larger excess of albumens. It may be interesting to point out that this is exactly the food in which I exceeded, and which furnished the uric acid for my subsequent troubles in fig. 65, though I would remark that had I been in a warm climate I should not have had nearly as much retention as is there shown (and my retention is much greater in the cooler portions of the year and little or nothing in the warmer); and further, I should probably not have had the gout of fibrous tissues which it eventually produced, as this was more or less the direct result of the determining action of cold.

But supposing in a warm climate I had by some means got an excess of uric acid into my body, I should have had as a result of the warmth and the increasing alkalinity of the blood, a plus excretion of uric acid with high blood pressure, headache and mental depression as its results, and possibly, if there was enough of it, some gravel or calculus as well, and it is these latter diseases that the natives of warm climates suffer from, and little, if at all, from gout, though, as I have previously mentioned, the uratic arthritis called rheumatism is by no means unknown in India.

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With regard to some of these points Surgeon-Captain Roberts says, in the letter to the *British Medical Journal* above referred to:—"Out of a total of over 4,000 cases of calculus operated on annually in India, one-half are reported from the Punjab, in a population of 20 millions, 1 million of whom are reported by Hunter as rice eaters, 97 per cent. of the arable area being under wheat, barley, and millets. Next come the North-West Provinces, with less wheat, but still only 3 per cent. of the cultivable area under rice, which is said (Hunter) to be eaten by 4 millions out of the 47 million inhabitants—a doubtful point to anyone who knows the North-West Provinces—and from this area from 900 to 1,000 stone cases are reported annually; thus three-fourths of the cases are reported from a wheat-, barley-, and millet-eating population of about 70 millions (or fewer).

"On the other hand, the ratio of calculus incidence to population is lowest—and there is a huge contrast between lowest and highest—in Bengal, Madras, and Burmah, where rice is the most important food staple. The contrast is seen even in one provincial area, namely, Lower Bengal; for Behar, the western part thereof, which is pre-eminently a wheat-producing and wheat-eating country, furnishes altogether a disproportionate number of the cases in the Bengal statistics.

"In this connection I must add that I have definite statistics from the Punjab dispensaries, showing that out of a total of 1,446 cases 1,199 were Mohammedans, and only 247 Hindus, a ratio of 5 to 1. These cases were not picked out to demonstrate a foregone conclusion, but are taken as reported. It is difficult to explain this special proclivity of Mohammedans unless the food factor be taken into consideration."

One further fact of interest came out in the above correspondence and discussion, namely, that the ratio of women to men in stone is very close to the ratio of women to men in gout; for if there is any truth in the pathology I have been endeavouring to defend, this must of necessity be the case, for when the urates are in the body they may have arthritis, and when the same urates are being dissolved and passing out of the body they may have gravel or calculus. They are but two stages of one process, and the ratio of women to men affected will almost of necessity be much the same for each.

In India, owing to the effects of warmth on the alkalinity of the blood, plus excretion of urates is the rule, retention the exception, a fact also mentioned by Surgeon-Captain Roberts in his paper on

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"Calculus"; and there men and boys suffer most from stone because they eat most meat and most albumen.

In England, with its cold climate, high acidity of urine, and low alkalinity of blood, retention of urates is the rule and plus excretion the exception—an exception associated mostly with the debility of advancing life; and here men suffer most from gout because they eat more in quantity; also, in my experience, more—often much more—meat than women; so that they have both excess of albumen and excessive introduction of urates.

And Sir A. Garrod remarks ("Gout and Rheumatic Gout," 3rd edition, p. 212) that when, in the degenerate days of the Roman Empire, women lived like men, they became "the subjects of acquired gout equally with men."

There seems to me in all this just nothing to necessitate the continued existence of "the uric acid diathesis," though doubtless many will still regard it with some affection, because for quite a large number of years it has played the part of a very respectable and convenient cloak for considerable ignorance.

The publication of the above correspondence also brought me a most interesting contribution of experiences from Surgeon-Major T. Holmested, formerly civil surgeon at Hyderabad Sind, which he has kindly given me leave to mention. Thus he says: "In Sind all Hindus but Brahmins eat goat and fish and lentils. Stone is very prevalent even in girls. I used to attribute it to chill, for I have had suckling infants with stone (the youngest he ever operated on being 14 months old).

"In Sind and North India in the cold weather the night and early morning is piercingly cold and midday hot—little children go about naked; the chill, I thought, upset the action of the liver. Enlarged spleen very common in Sind, and fever and pneumonia in cold season."

He also says that fruit and vegetables are deficient in the diet, at least for a great part of the year in a great part of Central Sind, and that amongst natives a modified scurvy, as shown by the teeth, is common.

I think that Surgeon-Major Holmested is quite right about the effect of chill, which may affect the active metabolism of a child very powerfully; in them cold will act as a stimulant and raise the acidity of the urine; it will probably diminish for several hours the natural morning excretion of urates, causing retention either from day to day or throughout the whole cold season.

The uric acid thus held back will come out either at some other

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hour of the day or at the end of the cold season with a rush, just as appears to occur in this country in March, April, and May, and on to July, and the result may often be insufficient solution and deposition of gravel or calculus.

The effects of fevers, pneumonia, and enlarged spleen in causing increased retention of urates in the body I have already mentioned several times; and a deficiency of fruit and fresh vegetables and the alkali they supply, will obviously help the other causes making for retention or accumulation, which in this country, just as in India, furnishes the material for subsequent gravel or stone.

In this country, on the other hand, we get some retention, that is, men and boys may sometimes go on introducing excess of uric acid in their food and yet not passing excess in their urine; but then some accident occurs and lays them up, they get a fever, a disease like splenic leucocythæmia, or, later in life, carcinoma, and down goes nutrition and up goes the alkalinity of the blood, and all their urate accumulations pass through it in such quantity as to cause more or less deposit in the urinary passages, as occurred in the case mentioned by Dr. Brunton, p. 43, or the case on p. 111, or the migraine case on p. 206. Some are very fond of the idea of washing out uric acid from the body and passages by drinking large quantities of water, but I cannot see any evidence that this is of much value. For we see from fig. 3 that considerable quantities of fluid taken in the morning hours do not pass through the kidneys, but remain in the blood till uric acid comes below urea in the afternoon, and yet it is exactly in the morning hours that most uric acid is excreted, and most water is required to wash it out of the urinary passages.

I think, therefore, that it is very little use to give large quantities of water, for it gets through the kidney just when it is not wanted, and it cannot get through the kidney when it is wanted, *i.e.*, when large quantities of urates are passing into the urine. Again, the drinking of much water may increase the excretion of uric acid by causing dyspepsia, hydræmia, or both, and thus do harm in gravel and calculus, where our aim should rather be to diminish for a time the excretion of uric acid, and at the same time free the excretion of water, as with an iodide.

Now, when an excess of water (*i.e.*, in excess of normal thirst and the requirements of the blood and tissues) is taken it often causes very marked dyspepsia, possibly by diluting the digestive secretions, and dyspepsia, as we know, causes uricacidæmia and a plus excretion of uric acid in the urine; but in gravel and calculus

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this is a harmful and not a helpful effect. And, apart from gravel, in other conditions of uric acid disease, I see no reason to think that water drinking in excess is of any real value in treatment, for, as we have seen in previous chapters, it is the uric acid that controls the excretion of water, and not the water that controls the excretion of uric acid.

Apart from the dyspepsia it may produce or increase, I doubt whether an extra pint of water swallowed has any effect on the excretion of uric acid in the hours which follow its ingestion: but where people habitually over-eat, it may be useful in default of other measures to cause a little dyspepsia and perhaps some increased action of the bowels, so as to sweep out some of their unnecessary supplies before they are digested and absorbed. As an amusing patient said to me some years ago, "What a world it is, one half dying of too much to eat and the other of too little," and in all uric acid diseases it is far easier to prevent introduction than, having got it in, to provide for its safe and satisfactory removal. The excretion of uric acid is controlled by its solubility in the blood, and, so far as I know, apart from dyspepsia, excessive water drinking affects this but little, and though as previously pointed out with reference to Sir W. Roberts' results in chapter xv., the more water there is in the blood the greater power it will have of dissolving bi-urate deposits, still if such urates are in this way brought into the blood in any quantity and assume the colloid form, they will obstruct the capillaries of the kidneys and allow only a scanty excretion of water to pass with the urates into the urine.

The effects of exercise on nutrition, metabolism, and the excretion of urea and uric acid I have already gone into at great length in chapter viii., and from the fact that it stimulates and increases metabolism, and improves the circulation through almost all the organs and tissues, it is easy to understand that regular exercise, short of fatigue, should be extremely useful in many of the disease processes of which I have been speaking. Thus in high blood pressure and headache it frees the capillaries and relieves the intra-cranial pressure; in mental depression Professor Lange has specially pointed out its value; then want of regular exercise is one of the most common causes of dyspepsia, with all its train of bodily and mental ills. Again, in albuminuria and glycosuria so much regular exercise as will keep up the nutrition of the skin, the muscles, and the important glands, is often one of the chief points in treatment. In gout also, as we have seen, regular exercise will prevent attacks.

In many cases, then, I consider such regular exercise as second

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only in importance to diet, and the two can often be employed together with advantage. Where the surroundings or the condition of the patient prevent satisfactory exercise, massage, which is, in many respects, equivalent to exercise, may take its place, and especially where nutrition is low, it is often an important help at the commencement of treatment. Then, again, massage is extremely useful, as has been so ably demonstrated by Dr. A. Symons Eccles,[1] in improving the circulation and nutrition in joints and other structures which have been damaged by urates, or have had their nutrition seriously affected by the circulatory changes which these substances produce, thus completing the cure of which the removal of the urates is only the first step, for obviously the removal of urates, while perhaps preventing further structural or nutritional change, will not restore the tissues to their original healthy condition. It is important, however, to bear in mind, as suggested in previous chapters, that massage, by flooding the injured fibrous tissues with fresh blood, and fresh and more alkaline serum, may really help considerably with the removal of urates from the tissues and the suspension of the chronic irritation, fibrosis and stiffening which their presence produces and keeps going; and this may apply equally, whether the original injury of fibrous tissues was uratic or traumatic, or as so often happens a mixture of both. And this constant presence of irritating urates may really account for much of the observed difference in the rate of repair of wounds and injuries between those who eat meat and those who live on an almost entirely uric acid free diet, the other most important factor being an improved circulation in the absence of collæmia. On the other hand, it is also true that exercise will do little or nothing for the relief of uric acid diseases so long as diet is left unaltered and uric acid is being continually introduced into the blood in excess.

Looking to all these facts it is most difficult to avoid the conclusion that all sufferers from the diseases treated of in this volume owe their sorrow, suffering, and early death to nothing in this world but their own folly. Certainly they have no right to blame nature either as to the origin of the troubles or their inheritance; in human nature, just as elsewhere in the Cosmos, the punishment follows the broken law, and comparative anatomy should long ago have warned them of their error in diet.

[1] *British Medical Journal*, 1888, vol. ii.; *Ibid.*, 1891, vol. i., p. 1,075; "Sciatica," Macmillan and Co., 1893; *Lancet*, 1893, vol. ii., p. 924; and "The Practice of Massage," Macmillan, 1895.

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That it is easily possible to sustain life on the products of the vegetable kingdom needs no demonstration for physiologists, even if a majority of the human race were not constantly engaged in demonstrating it; and my researches show not only that it is possible, but that it is infinitely preferable in every way, and produces superior powers both of mind and body.

Lastly, there is the extraordinary and almost inexplicable fact that most of the advantages of a diet from the vegetable kingdom have been pointed out by one man after another for well on to three thousand years, and their words have apparently fallen on the almost absolutely deaf ears of the meat eaters; from which we may perhaps conclude that the ingestion of these poisons blinds the eyes of its consumers to knowledge and wisdom, and prevents them realising that they and their fellows are constantly suffering many and terrible things for no reason.

It is true, however, that this knowledge of the ancients was very imperfect, so that in running from one danger they must have often fallen into another. Hence, such success as can now be attained, is to a corresponding degree an exact measure of knowledge, but there is still plenty to do in improving both.

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CHAPTER XVIII.

Instruments and Methods.

It is not my intention to devote space to a general consideration of instruments and methods; I shall merely state shortly those I have used, with a few remarks as to what I think about them.

Acidity of the urine can be estimated with a graduated solution of soda, of which 1 cc. = 6·3 millegrammes of crystallised oxalic acid, and a solution of phenol-phthalein, which gives a pink colour in alkaline solutions.

Process.—10 cc. of urine are placed in a small china saucer, and a drop or two of the phenol-phthalein solution added. The soda solution is then run in from a graduated pipette till a slight pink tinge is permanent. The amount of soda solution used is then read off, and multiplied by the number of 10 cc. in twenty-four hours' urine, and this worked out gives the total acidity of the twenty-four hours in grammes or grains of oxalic acid, and this is the way it is recorded in my curves.

Urea.—For this I have used the apparatus of Dupré, which can be obtained from Messrs. Griffin and Sons, Garrick Street, W.C. Its essential point is that the inner tube which collects the gas has two openings at its upper end, one communicating by a rubber tube with the reaction bottle, and another ending in a short rubber tube, which can be clamped just before using, when all the levels have been adjusted.

The chemicals required are a saturated solution of caustic soda and some bromine, which can be obtained in glass tubes containing the exact amount used (2·2 cc.).

Process.—Measure 22·8 cc. of the soda solution, and place it in the reaction bottle. Drop in a bromine tube so that it breaks on coming in contact with the bottom of the bottle; remove the broken glass, and mix the chemicals by shaking round and round. The result is a pale yellow solution, which is now ready for use, though if it is at all warm it should first be allowed to cool.

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Measure 5 cc. of urine into a small tube about two inches long, supplied with the reaction bottle; place it gently with a pair of forceps inside that bottle; adjust the cork in the bottle, and lower the inner collecting tube till the water stands at the line marked 0; lastly, clamp the upper tube of the collecting tube. Now take up the reaction bottle, and incline it to one side so that the urine in the little tube and the hypobromite solution mix, and continue to move the bottle from side to side for a minute or two till they are thoroughly mixed and the resulting effervescence is over. Place the reaction bottle on the table, and allow five minutes or so for it to cool, then raise the inner tube so that the water stands at the same level both outside and in, and read off the amount of gas on the graduations of the inner tube, which is so arranged that it gives, not the quantity of gas, but the percentage of urea which has been calculated from it. Say that the percentage on the tube is 1·5; this must be corrected for temperature and pressure, and the method of doing this can be found in any general work on physics.

It is important to see that the bung or cork and the tubes fit well, and continue in good order; this can easily be tested by raising the inner tube and clamping its openings when it is full of air; it can then be lowered into the water, and if the fluid rises into it, gradually replacing the air, there is a leak, which must be found and repaired.

Uric Acid.—The process originally described by Professor Haycraft in the *British Medical Journal*, 1885, vol. ii., p. 1,100.[1]

Apparatus.—A water or mercury suction pump to be obtained from Griffin or other instrument makers.

A flask fitted with a rubber bung perforated in two places. A small funnel is fitted into one of these perforations, and an elbow tube into the other.

The elbow tube communicates, by means of a rubber tube, with the suction pump, and the funnel is half filled with broken glass, the surface of which is shaken level, and then a pulp of asbestos, shaken up with water, is poured on to it, and the water allowed to run through while the suction pump is worked, till a uniform felt of asbestos ¼ inch thick has collected on top of the broken glass; this

[1] NOTE.—This process will be found given in Hoppe-Seyler's "Handbuch der Chemischen Analyse," p. 359, Berlin, 1893; Hammarsten's "Lehrb. der Physiolog. Chem.," 2nd edition, Wiesbaden, 1891; Neubauer and Vogel's "Analyse des Harns," last edition; Sutton's "Volumetric Analyses"; Sheridan Lea's work, "The Chemical Basis of the Animal Body"; and other text-books of physiology.

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is further washed by passing distilled water through it till the washings are clear of fibre, and then the filter with suction pump attached are ready for use.

The other things required are several glass flasks of 100-200 cc. capacity, a 10 cc. and a 50 cc. measure glass, and several pipettes graduated to $\frac{1}{2}$ cc.

The following chemicals are necessary[1]:—

Bicarbonate of soda.
Strong ammonia sp. gr. ·880.
Ammoniated silver nitrate solution.
Special dilute nitric acid.
Ferric alum, a saturated solution.
Centinormal ammonic thiocyanate solution.
Strong solution of common salt (Na. Cl.).
Bottle of distilled water.

All being ready, a sample of 25 cc. of the 24 hours' urine should be measured out and placed in a glass flask.

Before doing this I always note the colour, clearness, specific gravity, and the acidity (as above) from the whole bulk. If there is a turbidity or a deposit of urates, and if, as is generally the case in these circumstances there is a high sp. gr., *i.e.*, above 1020, I generally add to the whole bulk an equal volume of warm water, which, as a rule, clears it completely.

If in addition there is a deposit of red pepper crystals at the bottom of the collecting glass (and it is well to have a 3000 cc. glass jar graduated to 50 cc. and fitted with a bung for collecting the 24 hours' urine), I generally warm the whole bulk of the urine, adding some bits of solid caustic potash (the acidity having been previously estimated), and shaking till it is clear that all the uric acid has passed into solution.

A 25 cc. sample is then taken, and it must be cooled by placing the flask in cold water before proceeding.

To this add bicarbonate of soda (Haycraft says 15 grains, Herman says 30), and I am in the habit of adding about 30 grains or a trifle more, then 2 or 3 cc. of the strong ammonia, and about 2 cc. of the ammoniated silver nitrate solution. This last brings down a gelatinous precipitate of urate of silver, and if there is much of it the fluid is quite thick, and rapidly comes to rest after shaking round the flask.

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[1] These chemicals, with directions for carrying out the process, can be obtained from Messrs. Savory & Moore, 143, New Bond Street, W.

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If the patient is taking an iodide it will be necessary to add far more of the silver solution than the 2 cc. mentioned, but I will return to this point again.

We have now a precipitate of urate of silver, together with silver not combined with uric acid in an alkaline solution; the next process is to separate the silver combined with uric acid from that not combined with it.

The liquid containing the precipitate is now thrown on the filter, and the suction pump put in action; the gelatinous urate of silver remains on the filter, the fluid passes through, and the urate on the filter is washed with distilled water till the fluid passing contains no trace of silver.

The best way to ascertain this is to take two test tubes, and in one of them place 1-2 cc. of salt solution, and then pour into both test tubes some of the liquid passing through the filter. So long as the liquid in the tube with salt solution is distinctly more turbid than that in the tube without salt solution, more washing is required.

When the urate precipitate is thus got quite clear of uncombined silver, the special nitric acid solution is poured over it, filling the filter up to the top, and keeping it full for a minute or two by pouring a little more on as it runs down.

As soon as all the nitric acid with the urate of silver in solution has run through, fill the filter up with distilled water, and let that also run through, and we are now ready for the final stage of the process.

Take the flask containing the urate of silver dissolved in nitric acid and water, detach it from the suction pump by removing the rubber bung.

Add to the solution two or three drops of the ferric alum solution (indicator) and run in from a graduated pipette the ammonic thiocyanate solution till a permanent pink colour is produced. Read off the amount of thiocyanate used in cc., say it is 18 cc.: then 18 × ·00168 gives the amount of uric acid in 25 cc. of urine, *i.e.*, ·03024 grammes, and this multiplied by 4 gives grammes in 100 cc. = ·12096, and this multiplied by the amount of urine passed gives the total uric acid for the 24 hours in grammes.

When the urine contains iodides, the silver combines first with the iodide, and second with the uric acid; in other words, till enough silver has been added to combine with all the iodide present, urate of silver is not formed, so that if only the ordinary quantity of the ammoniated silver nitrate solution is added, the amount of uric acid may be greatly under estimated.

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The best way out of this difficulty is to add at once 4-6 cc. of the silver solution, then to filter and add to the filtrate more silver solution and see if any more iodide of silver comes down; if it does filter again, and again add more silver; when iodide ceases to form on the addition of the silver solution, add 2 cc. of that solution and filter finally; you will now get all the uric acid combined with silver and retained on the filter, and you can then proceed as before.

By this process, which I owe to the kind suggestions of Mr. J. E. Saul, F.I.C., I have been able to obtain the same amount of uric acid from a urine both before and after the addition of an iodide.

Haycraft's process takes from thirty to forty minutes to complete; longer for high sp. gr. urines, shorter for dilute, for much urate of silver clogs the filter and greatly increases the time required for the washing process; so that time is saved by diluting high sp. gr. urines; but when a urine of sp. gr. 1025 is diluted to 1 in 4, there is probably some increased loss of urate in the washing process, as the gelatinous urate clogs the filter and aids its own filtration, which, up to a certain point is more perfect the more there is of it.

I think that Haycraft's process thus described, while taking quite a moderate amount of time, gives very accurate and constant results; where there is any doubt I repeat my observation, and very rarely find a difference of more than ½ cc. of thiocyanate solution between the two; if there is a greater difference than this I go in for further investigation, and may find that a fragment of glass has perforated the asbestos and put the filter wrong, and when this has been put right I again repeat my observation.

Though the process takes thirty to forty minutes to complete, a large part of that time it requires only an occasional look to add water when it runs through, and other matters can be attended to, and then if the suction pump is powerful, several filters can be connected with it and several urines worked through at the same time.

It is, I think, a distinct advantage of this process that it can be worked on 25 cc. or even 12½ cc., of a high specific gravity urine, for when the urine of a single hour or less, which you may want to estimate in a case of headache, fits, or paroxysmal hæmoglobinuria, amounts only to some 20 or 30 cc., processes which require 50 or 100 cc. of urine cannot be used, and it would by other processes often be quite impossible to estimate the uric acid in small quantities of blood, muscle, or other organs which can be done by this process.

To estimate the uric acid in organs and tissues, I have used a

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process given by Salkowski and Luebe ("Die Lehre vom Harn," p. 94) for blood.

It consists simply of throwing the blood or tissue finely divided (I pass solid tissues through a mincing machine) bit by bit into ten times its volume of boiling water. The coagulated albumen is removed by filtration or decantation, and the fluid evaporated down to about the bulk of the original blood or tissue. I then apply Haycraft's process just as for urine (see remarks on p. 8).

As I found that long boiling of tissues appeared to increase somewhat the amount of uric acid obtained from them, I adopted the uniform plan of boiling for half an hour after all the tissue is in the boiling water.

It is by this process that I obtained the results given in chapters ii. and xvii. When tissues contain uric acid visible under the microscope or to the naked eye, this process yields a very large quantity, and the final evaporation need not be carried so far.

Supposing, however, that such great accuracy is not required, and that for clinical purposes all one wants to know is that a patient is passing about half as much uric acid again to-day as he was yesterday, or that the urine which was excreted at the time of a fit or headache or an attack of paroxysmal hæmoglobinuria contains two or three times as much as that passed in the previous hour when these troubles were absent, this knowledge can be arrived at in a very few minutes and without much trouble.

I have been pointing out now for several years that the urinary water is both from hour to hour and day to day inversely as the uric acid excreted along with it; by measuring the water from hour to hour, we can estimate the uric acid greater or less excreted along with it.

If the water in any hour is twice as much as in the previous hour, the uric acid will probably be only one half of what it was, or *vice versâ*, provided there is some water in the body to be excreted, and provided there has been no hæmorrhage, vomiting, or diarrhœa to remove all the available water from the body.

Taken over a long period of time, my lowest excretion of water is about 700—800 cc. in twenty-four hours, or about 30 cc. an hour, and with this the excretion of uric acid in relation to urea varies from about 1—18 up to 1—25.

On the other hand, my largest excretion of water is about 2000 cc., or about 80 cc. an hour, and this corresponds to a relative excretion of uric acid of about 1—35 to 1—45.

In single hours the excretion may fall below 30 cc., or rise a

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good deal above 80 cc., but the urine is most scanty in those hours of the day in which the excretion of uric acid is greatest, and most profuse in those in which it is least (see fig. 3.)

If at any time when the urine is scanty there is a doubt whether this is due to uricacidæmia and retention of water (*i.e.*, if there are no other signs of uricacidæmia being present), the blood should be examined, and if the scanty urine is due to uricacidæmia and retention of water it will be found to be dilute (*i.e.*, both hæmoglobin and red cells will be relatively diminished), but if the scanty urine is due to want of water in the body, it having been removed by the skin or bowels, &c., then the blood will be concentrated (*i.e.*, both hæmoglobin and red cells will be relatively increased). In this case no inference can be drawn from the urinary water as to the presence or absence of uricacidæmia.

But bearing these things in mind, if at any time, as often occurs in the uric acid headache, epilepsy, or hysteria (see case records in chapter vii.), the urine is 30—40 cc. in one hour, and 100 cc. or above in the next hour, no fluid having meanwhile been swallowed, if the urea is estimated in both hours, one will probably not be very far out if one puts uric acid as 1—20 of urea in the first hour and as 1—40 in the second, and precisely the same if the water fluctuation occurs in days instead of hours.

For many clinical purposes, and when the uric acid excretion is not required in grains for publication, this is all that one wants to know, and I am in the habit of thus reasoning from the water to the uric acid in scores of cases which I should have no time to estimate; making an estimation here and there to support my inference, if there seems to be any reason to doubt it.

Then again, as pointed out with reference to fig. 5, the difference between the temperature in the mouth and that in the rectum will often give a very decided indication of the quantity of uric acid in the blood, and when this agrees with the record of the urinary water there is not much room for doubt.

Lastly there seems to be reason to believe that the quantity of uric acid or xanthin present may perhaps be demonstrated in the blood itself (see p. 408).

Blood Decimal.—I have estimated the cells and hæmoglobin with the hæmocytometer and hæmoglobinometer of Dr. Gowers, and the decimal spoken of by Dr. A. E. Garrod and others as "worth," is obtained by dividing the percentage of hæmoglobin by the percentage of red cells, thus $\frac{\%\text{ Hæmoglobin}}{\%\text{ Red Cells}}$ if both are at the supposed normal (100), the result is a whole number, and not a decimal, but as this

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is only very rarely the case a decimal is generally obtained which represents the hæmoglobin value of each red cell. This is low as ·3 in chlorosis, and ·6 to ·7 or above in more normal conditions.

From this decimal with daily observations a curve can be constructed comparable with the curves of uric acid and urea excretions (see figs. 43 to 52 and 65.) And with similar daily observations, it will be found that when there has been a diuresis both the cells and hæmoglobin are increased as regards the given quantity, while, when fluid is being retained in the body (dropsy), they are both diminished as regards the given quantity, and the daily excretion of uric acid can be roughly estimated from these facts alone.

But the greater or less quantity of water in the blood does not directly affect the value of the blood decimal, though when excess of water is due to excess of uric acid (uricacidæmia), the blood decimal will be found to fall.

A new hæmoglobinometer and hæmocytometer has been brought out by Dr. Oliver, the inventor of the arteriometer, to be presently mentioned. The hæmoglobinometer is an adaptation of an instrument used commercially for determining shades of colour. It has to be used by the light of candles of constant power.

The hæmocytometer depends on an observation by Dr. Oliver that the appearance of the reflection of the candle as a streak of light through a mixture of blood and diluting fluid in a special tube, always corresponds with the presence of a definite number of cells, hence the tube can be graduated in per cents. to correspond with the dilution required to bring out the streak of light.

I have used both these instruments, and compared them with those of Dr. Gowers', and I find Dr. Oliver's hæmoglobinometer very useful in the dark days of winter, when one has to work by artificial light, but on the whole I prefer Dr. Gowers' instrument when daylight is available. Dr. Oliver's hæmocytometer is easy to work with when you have got into the way of using it; the results are fairly quickly obtained, and with care appear to me to come very close indeed to those obtained by counting with Dr. Gowers' instrument.

Water in Expired Air.—I have estimated this by means of U tubes filled with calcium chloride; each arm of the tube is about eight inches long, and has a diameter of a little less than one inch. It is closed at each end by a rubber bung perforated by a glass tube bearing a bit of rubber tubing and a glass mouth-piece on one end; the rubber tubes are closed by spring clamps. The whole is carefully weighed before use and again afterwards, and the difference re-

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corded equals the moisture in the expired air. It is used as follows :—

Remove the clamp from the rubber tube at the far end of the U tube, and place the glass mouth-piece on the near end between the lips. When respiration is quite regular, and sitting quietly and comfortably, and the second hand of a watch is at a given place, begin to expire through the tube between the lips, inspiring through the nose; the clamp on the near tube is to be opened at each expiration and closed at its end. After a little practice it is possible to continue to respire quite regularly, and to open and shut the tube at the right moment in each act. This is continued for five minutes by the second hand of a watch on the table, the clamp is then shut and the distal tube also clamped, and the tube is ready to be weighed.

I may say that Messrs. Savory and Moore kindly did the weighing for me, as I have no instruments sufficiently accurate.

I measured the urine passed in fifteen minutes, including the five minutes of expiratory estimation, and divided the result by three to compare with the expired water in five minutes.

The results show that when the urinary water is scanty owing to uricacidæmia, the expired water is also scanty, and this affords the best proof that uric acid affects the capillaries in the lungs as well as those in the kidneys and elsewhere throughout the body.

Pulse Tension or Blood Pressure.—Apart from the signs to be obtained by an educated finger on the radial artery, and an educated ear at the apex and base of the heart, the sphygmograph furnishes the best clinical record of arterial tension, and has this further advantage, that the tracing can be kept indefinitely for comparison with all future tracings.

By pulse tension one practically means blood pressure, or such blood pressure as results from contraction of arterioles or blocking of capillaries on the one hand, and the pumping power of the heart on the other.

There is no doubt that the sphygmograph is but an indifferent gauge of blood pressure, but it tells us what is clinically of far more value—the effects which contraction of the arterioles and obstruction of capillaries produce on the heart and large vessels behind them; that, in two cases lying side by side, the actual blood pressure may be identical; but in one case, say, with a well-nourished and hypertrophied left ventricle, it may be produced by a slight contraction of arterioles or obstruction of capillaries, while it produces almost no effect, except a little slowing of the heart's action; in the other

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case, with an ill-nourished heart, the pressure may be produced by very great obstruction of capillaries, while the heart is acting irregularly, palpitating and fluttering, in a word, failing and dilatating, before the peripheral resistance; all this the sphygmograph will tell us with considerable accuracy, while to be told that the blood pressure is the same in these two cases, is information of almost no clinical value.

I have used the sphygmograph of Dudgeon, and recently I have had one fitted with a pen, the invention of my friend, Mr. W. H. Symons, which I believe to be a great improvement on the old point scratching on smoked paper.

The pen consists of a little cone of metal, open at both ends, and threaded with a bit of cotton. The small end of the cone with the cotton below it rests on the paper, and is moved over it in exactly the same way that the old point was moved.

The only thing to attend to is that the paper must be highly glazed and very smooth, to reduce friction, and then the pen runs over it perfectly, making curves which are identical with those obtained by the old process. The instrument thus modified, with directions for use, can be obtained from Messrs. Maw, Son, and Thompson, London.

The pen works best with a solution of aniline, a little of which is placed on the upper end of the little cone, and is conducted down by the cotton.

In this way there is no limit to the number of tracings that can be taken, as paper after paper can be passed through the machine, so as to catch irregularities of the pulse, which only occur now and again, or a continuous tracing can be made on paper several feet long. The tracing is permanent from the moment it is made, and there is no black to rub off, and no fixing required, so that this useful invention renders the process both more cleanly and more expeditious, and is a great help to clinical recording. I have already mentioned Dr. Oliver's inventions—the arteriometer and the pulse pressure gauge—to be obtained from Mr. Hawksley, of Oxford Street, and have said that I believe they may be found to be of very great clinical value for recording changes of blood pressure produced by uric acid, or by drugs which act upon it, and have given some instances in which this appeared to be so. My results, so far as they go, are very favourable to their accuracy and the value of their records; and it will be seen that I have used the arteriometer in several figures and elsewhere to obtain indications of blood pressure.

One is no doubt liable to make errors with the arteriometer by

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not getting exactly over the artery, which one may manage fairly well on one occasion and not on the next; but this error is always on the side of making the diameter of the artery appear too great, so that the smallest reading to be obtained is the most correct, and the best way is to make repeated observations with the object of obtaining this. My results with this instrument generally agree among themselves, like conditions yielding like results, and also with the changes in the rate of the heart's action and of the sounds at the apex and base. Of the three I regard the changes in the rate of action as the best guide in physiology, so constant and true is Marey's law; but when all three agree there is not much room for doubt that the diameter of the artery has been correctly measured.

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